TYPHOID FEVER IN ABERDEEN

A CRITICAL ANALYSIS

by

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PREFACE

In May 1964 I was a house-physician in the City Hospital, Aberdeen, when an outbreak of typhoid fever began. This hospital is the fever hospital for Aberdeen and consists of several separated wards with a total of 231 beds. Because of a shortage of senior staff I was involved in admitting and caring for the vast majority of the typhoid patients during part or all of their stay in hospital.

My duties were partly clinical and partly administrative. A "Typhoid Co-ordination Centre" was established, of which I was in charge; the functions of this centre were initially to facilitate the admission of patients by general practitioners to the various hospitals involved and to advise the general practitioners and the Medical Officers of Health by telephone of all positive laboratory findings. Later the same centre controlled the clearance programme of all typhoid patients, co-ordinated the clinical trial of ampicillin which was conducted in 4 different hospitals, and maintained a record of all laboratory investigations performed after the patients were discharged from hospital.

This outbreak of typhoid fever occurred in a country in which this disease is comparatively rare and is certainly not endemic. The chance that the course of the disease was influenced by previous exposure to typhoid infection was slight. When the wealth of data which accumulated during this time was finally examined it seemed to me that useful evidence could be obtained from this outbreak which might contribute, by way of certain limited conclusions, to the modern knowledge of typhoid fever and have some influence on present-day belief about the disease and its treatment. This thesis is therefore a series of short discussions on several aspects of typhoid fever, each illustrated by examples from the Aberdeen outbreak of 1964.

TABLE OF CONTENTS

LIST OF TABLES

14. Percentage distribution of occupied and retired adults in Aberdeen city and in the typhoid population by sex distinguishing social class.

15. Comparisons of the incubation periods of 378 typhoid patients.

16. Frequency of clinical features in the 469 typhoid patients.

17. Levels of 310 white cell counts on admission, distinguishing "severity of illness".

18. "Severity of illness" of typhoid patients distinguishing age and sex.

19. Incidence of complications in 469 typhoid patients.

Section III

20. Details of initial treatment used in Aberdeen Typhoid Outbreak 196

21. Treatment of patients who relapsed in Aberdeen " " "

22. Assessments of treatments " " " "

23. Relapse rates in chloramphenicol treated typhoid fever, quoted by various clinicians.

24. Comparison of patients who relapsed with other typhoid patients.

25. Comparison of patients with "post-treatment pyrexia" with other typhoid patients.

26. All children with a severe initial infection treated with chloramphenicol.

Section IV

27. Results of Army Field Trial 1904 - 1908.

28. Typhoid strains used in the British Army vaccines 1933 - 1960.

29. Comparisons of the incidence of enteric fever in 1914 - 18 and Boer Wars.

30. The results of field trials of acetone-dried and heat-phenolised

LIST OF FIGURES

Section IV

15. The effectiveness of acetone-dried and heat-phenolised vaccines as observed in controlled field trials in British Guiana, Poland, U.S.S.R. and Yugoslavia. (Source Cvjetanovic & Uemura, Bull. W.H.O.1965).

Section V

16. The clinical course of two volunteers who suffered asymptomatic typhoid bacteraemia. (Source Snyder et al. 1964).

Section VI

17. Mean level of "H" agglutination titres on admission to hospital related to day of clinical illness.

Section VII

18. The treatment of 159 convalescent excretors and outcome.

19. Natural rate of clearance in 42 patients.

SECTION I

A SHORT REVIEW OF TYPHOID FEVER

In this introductory section the history of typhoid fever since its recognition as a fever distinct from other continued fevers is reviewed. The growth of knowledge about typhoid fever is outlined with regard to its epidemiology, its causative organism, its prophylaxis and treatment, and its persistence by way of the carrier state. The incidence of typhoid fever in Britain and in Aberdeen in particular and the low incidence in these parts compared with other parts of the world is discussed. The present knowledge of the pathogenesis of typhoid fever and of the reaction of the host to infection is briefly described.

SECTION I

A. A SHORT GENERAL HISTORY OF TYPHOID FEVER

Few diseases have masqueraded under as many names, or have engendered as much argument, as typhoid fever. Murchison (1873) says that as early as 400 B.C. Hippocrates described "many cases of fever of the continual type characterised by diarrhoea, offensive watery stools, bilious vomiting, tympanites, abdominal pain, 'red rashes', epistaxia, sleeplessness or a tendency to coma", a description which, in the present day, can hardly be bettered. For many centuries, however, typhoid was confused with other fevers, under the generic name "Continued Fever".

(i) THE DISTINCTION OF TYPHOID FROM OTHER CONTINUED FEVERS

Although astute observers were aware of several varieties of continued fever, it was not until the late 16th century that distinct diseases were described. Typhus fever had long been recognised but since, like all fevers, it presented in many different ways, it had several other names, such as "spotted fever" and "gaol fever", each of which was thought to be a separate disease. In

1659/

1659, Thomas Willis described a fever which differed from typhus in being less contagious, showing fewer skin eruptions but more complications, and being accompanied by ulcers in the small intestine; this we now know to have been typhoid.

From this date on, there were a few observers who believed that typhus and typhoid were two distinct diseases. Gilchrist of Dumfries in 1734 wrote an essay on "Nervous Fever" which was an accurate description of typhoid as distinct from the "malignent fever of hospital", i.e. typhus. As recently as the early part of the 19th century, however, any continued fever accompanied by delirium was called "typhus fever". At this time both French and British clinicians began a detailed investigation of the pathological findings in cases of fever. It is easier to understand the subsequent controversy between these two clinical schools of thought if it is remembered that in France there was only one endemic disease of this kind - typhoid, while in Britain there were two - typhus and typhoid, the former being more prevalent.

In France, Prost in 1804 published autopsy findings on over two hundred patients and described intestinal ulcers which he said were common to all fevers. In 1813, Petit and Serres said that these lesions were confined to the ileum and called the fever associated with them "la fièvre entéro-mésentérique" to distinguish this/

this from ordinary enteritis. Bretonneau in 1820 went a stage further and stated that the lesions were confined to the glands of the ileum, i.e. the Peyer's patches. He considered, rightly, that they were due to a specific inflammatory poison and accordingly named the condition "dothiénentérite", i.e. tumour of the intestine. He also affirmed that the extent of the lesion did not depend on the severity of the associated fever. In 1829, Pierre Louis collated the findings of the French School and named the disease "la fièvre typhoide" which merely means the fever resembling typhus.

The French were also aware of the skin lesions of typhoid fever. Chomel, in 1833, gave an excellent description of them thus:-

> "The eruption, which is peculiar to typhoid fever, consists of small rose-coloured spots, disappearing on pressure, from half a line to two lines in diameter, round, not hardly elevated; scattered over the abdomen .....there should be at least fifteen or twenty."

Meanwhile observers in Britain, instead of finding intestinal lesions in all fatal cases of fever, could demonstrate them in only a few. Sutton in 1806 described an outbreak of fever in which the bowels were inflamed and gangrenous in fatal cases, and Hewett, in 1826, described ten cases of "follicular ulceration" of the bowel limited to the Peyer's patches, and stated that these were the same disease/

disease as the dothienenterite of Bretonneau. But these observations were unusual, and such lesions were thought by most workers in Britain to be merely a complication of typhus fever. However, in 1836 Robert Perry, a Glasgow physician, said that dothienenteritis "may occur in combination with the contagious typhus about once in every six cases or exist as a disease per se", and stated that in the latter type of case there was no "typhus-eruption". His work was continued by Stewart who, in 1840, was the first person in Britain to publish a clear differential description of the two diseases. He analysed cases in Glasgow and Edinburgh and distinguished between typhus and typhoid with regard to cause, clinical features including skin rashes*, and anatomical lesions. He said that, while typhus was associated with poor and crowded living conditions, typhoid fever often appeared in country areas and in well-ventilated houses.

Stewart was not, however, the first person in Europe to state that there were two separate diseases in Britain. In 1836 Lombard from Genova visited several towns in Britain and Ireland, and observed that there were "two distinct and separate fevers", one of them identical with the contagious typhus, which in France was epidemic, the other a sporadic disease identical with the endemic typhoid fever or dothienenteritis/

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* An interesting comment is made by Patrick (1955) when quoting Stewart's description of the two different red rashes; Patrick says: "the modern reader of these controversial writings is struck by the late appearance of any reference to the typhus rash, though not by the early failure to notice the elusive spots of typhoid. A possible reason is that the typhus petechiae were hidden among the bites of lice and fleas which must have been very common".

dothienenteritis of the French. Universal credit for the first clear differentiation goes outside Europe to Gerhardt of Philadelphia who, in 1837, pointed out the difference between the contagious typhus fever with its petechial eruption and the intestinal disease typhoid fever with its rose-coloured spots. He insisted that "the distinctive characters of the two diseases are such as in practice could not allow them to be confounded".

Back in Britain, medical workers were slow to accept the fact that typhoid and typhus fevers were different diseases, but were finally convinced by William Jenner who, between 1849 and 1850 analysed 66 cases of continued fever and divided them into 23 cases with ileal lesions and 43 without. His masterly comparison of the two groups included the clinical observations of gradual onset and longer duration in typhoid fever; its rose spots as opposed to the "mulberry rash" of typhus; and epistaxis, intestinal haemorrhage, abdominal distension and watery stools, all of which were present in typhoid and absent in typhus. He himself had suffered from both diseases, and he pointed out that each gave protection from a further attack of the same, but not from the other illness. Most important of all, he showed that the cases admitted to the London Fever Hospital came from different areas at different times and that one fever did not communicate the other. Thus, at last, he left no room for doubt that there were indeed two distinct fevers, typhus and typhoid.

(ii)/

(ii) MODE OF SPREAD

Until the 19th century, the general consensus of opinion was that typhoid fever was not contagious, although Willis in 1659 compared the gastro-intestinal ulcers which he found in some cases of fever to the pustules of variola and implied its possible spread from these ulcers. Much of the controversy which then arose was engendered by the use of the word "contagious" in two separate ways: firstly, in the literal sense of spread by touch or contact and, secondly, in the more general meaning of spread from one person to another by any means. Typhoid fever is contagious only in the second sense.

The first evidence that typhoid was communicable was produced by the French writer Leuret in 1828 when he described an outbreak of typhoid in Nancy and showed that every case could be traced to a stranger who had visited the city while suffering from the disease. Gendron reported a similar instance in France in 1834 and said that most cases became infected either by living beside, or by handling clothing or utensils of, a typhoid patient. However, these writers were unable to say how the infection was emitted from one patient and acquired by the next, and few clinicians accepted their findings. Gay (1918) states that of those who did, Canstatt, in 1847, was the first clearly to implicate the excreta as the vehicle of/

of spread of infection and that Riecke (1850) showed that some outbreaks could be traced directly to the ingestion of drinking water that had been polluted with sewage. On the other side of the Atlantic, Flint observed an outbreak in Boston, Massachusetts, in 1843 and noted that it appeared to have been due to the ingestion of water from a well which had been "poisoned" by a stranger who had died of typhoid fever while staying at the local inn.

The findings of the French workers were summarised by Piedvache in 1850. He concluded that typhoid was contagious, but only in so far as the word implied a spread from one person to another, by whatever means; he was still uncertain as to the exact mode of spread, and most clinicians remained unconvinced.

In the meantime, William Budd in England had seen many small outbreaks of typhoid and had come to the same conclusion; but Budd, probably the main contributor to modern understanding of typhoid fever, took the matter much further. In 1856 he said that "the sewer may be looked upon in fact as a direct continuation of the diseased intestine". He asserted that, in the majority of outbreaks which he had seen, the infection had occurred by overflow of sewage from an infected cess-pool to a nearby drinking well, the water in which was then consumed by people who developed typhoid fever shortly afterwards. He gave detailed accounts of cases to support this claim and he also affirmed that milk was sometimes the vehicle of spread.

Budd/

Budd recommended the following precautions to prevent the spread of typhoid fever:

"1. That for the future, all the discharges from the fever patient should be received on issue from the body to vessels containing concentrated solution of chloride of zinc.

2. That all infected bed or body linen should, immediately on its removal, be placed in water strongly impregnated with the same agent.

3. That the water closet should be flooded several times a day with it and that some chloride of lime should be placed there to serve as a source of chloride in the gaseous form.

And, lastly, and by way of further precaution, that so long as the fever lasts the water closet should be used exclusively as a receptacle for the discharges from the sick."

In his book published in 1873 Budd quoted instances where a convalescent patient had caused an outbreak, but said, "in what form the infection still lurked - whether in articles of wearing apparel ..... or whether in the form of specific exuviae from which the diseased intestine may not have entirely cleared itself, I confess myself unable to say". This appears to be the first time that/

that it was realised that infection could be transmitted even after the acute stage of the illness had passed.

Despite Budd's clear exposition, controversy was still widespread and this is illustrated by a quotation from Murchison who, in the same year, said, "all evidence is in favour of the view that the fresh evacuations are harmless and that the poison is developed during their putrefaction". However, it slowlybecame accepted that the theories of Budd were correct, and these have formed the basis of our present-day knowledge of the mode of spread of typhoid fever.

(iii) THE TYPHOID BACILLUS

In 1873 Budd wrote that "there is a growing belief that the specific germs which cause contagious fevers are in reality so many living species". In 1880 Eberth discovered the typhoid bacillus in the organs of cases who died of typhoid fever; Klebs, who also identified it in that year, gave it the name Bacterium (B) typhosus. Three years later Gaffky cultured B. typhosus outside the body, and since then it has been possible to obtain absolute proof of infection in suspected cases of typhoid. In the following few years B. typhosus was isolated from the living person or from the excreta by a number of people - from faeces by Pfeiffer (1885), from urine by Hueppe (1886), from rose spots by Neuhaus (1886), and from circulating blood by

Vilchur/

Vilchur (1887). In 1890 Gilbert and Girode isolated B.typhosus from the gall bladder of typhoid patients suffering from acute cholecystitis, a finding which greatly aided the understanding of the pathogenesis of typhoid fever.

B. typhosus is now known to be a member of the group of intestinal pathogens called 'Salmonella' and, therefore, it is now more usually referred to as Salmonella (S) typhi. It is a rod-shaped Gram-negative motile aerobic organism which does not ferment lactose or sucrose. In antigenic structure it contains 'H' or flagellar, 'O' or somatic, and Vi antigens, and these components stimulate the production of specific antibodies when the typhoid bacillus invades a host organism. The quantity of these antibodies in serum is measured by a test developed by Widal in 1896. The 'H' (hauch) meaning "breath" forms, and 'O' (ohne hauch) meaning "without breath" or non-spreading forms were first demonstrated in B.proteus by Weil and Felix in 1917. In 1920 Weil and Felix described the same factors in S. typhi and established that the heat-labile 'H' antigen was found in the flagella of the organism, while the heat-stable 'O' antigen existed in the body or soma. In 1924 Felix showed that the 'O' antigen was responsible for the pathogenicity of S. typhi. Felix & Pitt (193 discovered a second somatic antigen in some strains of S. typhi and named it Vi (for virulence) since he considered that it was responsible for the virulence of those strains which contained it. It has since been suggested (Bhatnagar et al. 1938) that Vi antigen exists on the surface/

surface of the soma of the organism forming a protective layer, and it is responsible for virulence only in as much as it protects the pathogenic 'O' antigen from destruction. (Felix and Pitt 1951).

In 1957 Archer and Whitby, using live vaccines representing the 'O' and Vi antigens, showed that the Vi antigen was responsible for the rapid death of mice from "intoxication", whereas the 'O' antigen was responsible for death after four or five days of illness with typical pathological changes.

In 1921 Arkwright detected 'rough' (R) forms of pathogenic intestinal bacteria. These forms are spontaneously agglutinable in physiological saline, whereas there are other stable forms which are 'smooth' (S). He also showed that these forms could interchange, S to R by prolonged incubation in one medium and R to S by frequent transfers from host to host. This phenomenon is characteristic of S. typhi and is known as S ⇄ R variation.

In 1936 Craigie and Brandon found that anti-Vi bacteriophages (viruses which grow in and destroy bacteria) could be grown which were specific for their strain of origin and thus could be used for identification of different strains of bacteria. This was the basis for a system of classification of S. typhi called Vi-phage typing, developed by Craigie and Yen (1938). This system is of immense value in epidemiology, as it can link otherwise unconnected cases to a

common/

common source. There are, to date, 72 different 'phage-types of S. typhi (Wilson and Miles 1965).

In 1896 Achard and Bensaude isolated an organism which produced an infection resembling typhoid fever but less severe. They called this bacterium B. paratyphosus, since it was similar to B. typhosus but produced different sugar reactions. There are several varieties of B. paratyphosus, or Salmonella paratyphi, as it is now generally known, but only S. paratyphi A and B cause human infections which are likely to be confused with typhoid fever.

(iv) RECOGNITION OF THE CARRIER STATE

Budd, as early as 1873, was aware that typhoid fever could be spread even after the end of the acute illness. He wrote, "I have seen so many instances in which fever has broken out in a family living in a previously healthy neighbourhood soon after the arrival of a convalescent, that I am quite sure that patients so far recovered cannot always be safely allowed to mix with others without precaution. In the case referred to, all traces of actual fever had disappeared and diarrhoea had long ceased".

The discovery of the typhoid bacillus in persons suffering from acute typhoid fever was followed closely by its isolation from the excreta of individuals who had recovered. Chantemesse (1891) found/

found S. typhi in the bile of a woman undergoing a gall-bladder operation eight months after an attack of typhoid. In 1895, Lazarus found bacilli in the faeces of a patient 41 days after the end of the acute illness and Horton-Smith (1897) found them in urine 70 days after illness. Thus it came to be realised that a convalescent carrier state could also exist.

In 1899 Houston reported a case of typhoid cystitis of three years' duration in a woman who had not suffered recognisable typhoid fever. She had nursed a child with diarrhoea who died, and shortly afterwards she developed intermittent frequency and dysuria; three years later Houston isolated typhoid bacilli from her urine and her serum showed "a positive reaction". Houston wrote that "it proves that the bacillus may occur in the tissues, and the blood serum give Widal's reaction, without the infection which we recognise as typhoid fever resulting." In 1902 von Drigalski and H. Conradi, on the advice of Robert Koch, who had found cholera vibrios in symptomless persons, examined healthy contacts of typhoid patients and found organisms in the faeces of four of them. In the same year Koch, who was probably the first person really to appreciate the danger of the carrier state, began a highly successful campaign to investigate and prevent the spread of typhoid fever in South-West Germany. He maintained that the typhoid bacillus was no longer viable after it left the human body and that infection/

infection was direct from man to man and, therefore, if patients and convalescent carriers were detected and isolated, the spread of infection would cease. To this end he set up several bacteriological laboratories whose function was to isolate cases and follow-up their contacts. The results of this campaign, published in 1912, showed that the incidence of typhoid had indeed fallen enormously, but it also demonstrated clearly the existence of many chronic carriers who could remain unidentified and be a source of infection. Klinger (1909) for example, found 431 carriers during the campaign in a population of just over two million.

The epidemiological significance of the carrier state was at last recognised, and throughout Europe attempts were made to identify typhoid carriers and prevent them from spreading the disease. In England the Army set up two camps in 1909, similar to those organised by Koch in Germany (Dawson 1965) while in Scotland Dr. A. Ledingham in 1908 found 3 carriers in an asylum in which typhoid fever had been a recurring problem for many years (Ledingham and Ledingham 1908).

Thus two public health measures could now be enforced: firstly, the prevention of spread of infection, both by improved drainage systems and by purification of likely sources of infection, for example water, and, secondly, the surveillance of typhoid carriers.

(v)/

(v) IMMUNISATION AGAINST TYPHOID FEVER

A third possible means of preventing the spread of infection was introduced at the turn of the century. In 1896 Wright in Britain, and Pfeiffer and Kolle in Germany produced a vaccine consisting of a killed broth culture of typhoid organisms. Wright inoculated British troops in India and the Boer War, and claimed a reduction of 50% in both the attack rate and the mortality from typhoid fever. After much initial doubt and argument Wright's vaccine, slightly modified, was accepted by the British Army and given to the majority of troops engaged in the First World War. It appeared to be successful in reducing the incidence of typhoid fever amongst the troops and its use was continued in all the British Armed Forces.

The vaccine first used was prepared by killing organisms with heat and preserving with phenol. In 1943 a new vaccine was introduced in the British Army in which the organisms were killed and preserved with alcohol in order to maintain a high level of the allegedly protective Vi antigen (Felix 1941). During the next five years, however, there were several serious outbreaks of typhoid fever amongst personnel immunised with either or both of these vaccines, and in 1948 a field trial of both vaccines was organised by the Army. Unfortunately the incidence of typhoid fever/

fever amongst troops fell suddenly and the trial was a failure, so in 1954 the first of a series of field trials was set up by the World Health Organization. Its aims were to discover:

(a) whether immunisation afforded any protection against typhoid fever,

(b) if so, whether any one vaccine gave better protection than another,

and (c) whether the effect of the vaccine in man corresponded to the results obtained in laboratory tests.

The results of the first two trials indicated that, for the vaccines used alcoholised vaccine gave no obvious protection, whilst heat-phenolised vaccine was 70 per cent effective in protecting individuals against an attack of typhoid fever. This demonstrated clearly that there was little or no correlation between the findings in man and those with laboratory tests, since the latter suggested that much higher protection was conferred by alcoholised vaccine. (Felix, Rainsford and Stokes, 1941.)

In further trials in Yugoslavia and in British Guiana in 1960-62 it was found that a third type of vaccine, namely acetone-dried, gave a 90% protection against an attack of typhoid fever, as opposed to 70% with phenolised vaccine. (Yugoslav Typhoid Commission, 1964; U.K. Typhoid Panel, 1964.)

Thus/

Thus, it would appear, firstly, that the use of antityphoid vaccine in man is justified and, secondly, that acetone-dried vaccine gives better protection than the phenolised product, both being more effective than alcoholised vaccine.

(vi) THE TREATMENT OF TYPHOID FEVER

Until the discovery of the antibiotic chloramphenicol, and of its value in typhoid fever (Woodward et al, 1948) many different treatments were advocated, but none proved of real benefit. The classical cold-bath treatment which was used in Roman times was still in vogue at the turn of this century (Hare, 1898). If the temperature rose above 102.2°F. the patient was immersed in a bath of water at 68°F. for about fifteen minutes. This certainly reduced the high fever and sweat loss, and gave symptomatic relief. Opium was also widely used, both to sedate the patient and to counteract the intestinal symptoms of typhoid fever. Salt was given, both externally and internally, by many clinicians during the 19th Century (Reid, 1827), but this fell into disuse during the earlier part of this century. With the appreciation of the dangers of salt depletion (Marriott, 1947) the use of salt on a rather more scientific basis was re-introduced in the 1940's.

Serum/

Serum therapy was apparently first used in 1895 by von Jaksch and Walger who injected into patients the serum of recovered cases of typhoid fever (Gay, 1918). Auto-serum therapy was also tried, i.e. subcutaneous injection of the patient's own serum, and was alleged to be sometimes of value if the level of circulating antibody was high at the time of withdrawal of the serum (Koenigsfeld, 1915). Chantemesse (1898) claimed good results with antitoxin prepared from a soluble exotoxin, while Besredka (1906) asserted that the serum which he prepared from endotoxin was much more effective. After Felix and Pitt (1934) discovered the Vi antigen, Felix prepared a serum containing large amounts of 'O' and Vi antigen, and reported that it was of value in the treatment of typhoid fever (Felix 1935). Several other observers agreed with this finding, for example Cookson and Facey (1937) used it in a large outbreak at Bournemouth in 1936 and found that it decreased the extent of toxaemia. However, Bell (1937) observed that it did not reduce mortality and could be dangerous and even fatal when given intravenously, as was recommended. It was never completely accepted as a method of treatment, and fell into disuse with the introduction of antibiotics.

Vaccine therapy was also tried by many workers after Fraenkel (1893) first used subcutaneous injections of killed typhoid cultures./

cultures. The results varied considerably; some observers thought it of value, others found it dangerous (Gay), and it was not generally adopted for use. In recent years it has again been used in an attempt to stimulate antibody production in the face of anti-:biotic therapy, since the latter is believed to suppress the formation of antibodies (Marmion 1952). This aspect of its use will be discussed more fully in Section III.

In general, then, the only accepted treatment for typhoid fever available in the first half of this century was symptomatic, with rest, fluid diet, and good nursing care to keep the patient comfortable and maintain his strength. With the discovery of sulphonamides and penicillin, these were hopefully tried, but with little or no effect. Then in 1948 Woodward et al. described the successful treatment of ten cases of typhoid fever with chloramphenicol, and this drug became the treatment of choice for the acute typhoid illness. Other antibiotics have since been tried, either alone or in combination with chloramphenicol, for example synnematin B. (Benavides 1955) and chlortetracycline (Huckstep 1962), but none is as effective as chloramphenicol alone.

Chloramphenicol brought about a dramatic fall in the mortality rate from typhoid fever. It also increased the problem of the typhoid relapse (Smadel et al. 1949). Modern research is now directed/

directed to the solution of this problem, which will be considered in greater detail later in this thesis.

Treatment of the chronic carrier state by conservative methods has been unsuccessful up to the present time (Christie 1964). Surgical treatment, in the form of cholecystectomy for faecal carriers and nephrectomy for urinary carriers if only one kidney is affected, has been moderately but not uniformly successful in curing the chronic typhoid carrier. Vogelsang and Boe (1948) summarised the results of cholecystectomy performed by several workers and stated that it cured approximately three-quarters of carriers. Drainage of the hepatic duct, to allow free flow of bile, was first performed successfully by Dehler (1907, 1912) and has since been recommended by several workers (Garbatt, 1922; Whipple, 1929). In 1960 Erlik and Reitler cured three carriers, operated on because of biliary colic, by cholecystectomy with drainage and irrigation of the common bile duct for one to three months, and it seemed possible that this combined method might cure a higher percentage of carriers than either [illegible] operation alone. However, some carriers will not submit to operation and others are not sufficiently healthy to withstand it, and the search has continued for a conservative cure of the carrier state.

A new antibiotic, ampicillin, which was discovered in 1961 (Rolinson and Stevens) proved to be effective in stopping excretion in a number of chronic carriers (Bullock 1962, Troy, 1963 [illegible] Christie 1964) and it was hoped that the carrier state could at last be cured./

cured. In view of this, a clinical trial of ampicillin in the temporary carrier state was conducted in Aberdeen, in order to discover whether it was effective in preventing the occurrence of the chronic carrier state. This will be described in Section VII of this thesis. In the event ampicillin has not proved to be as successful as was hoped.

The main problems, then, as regards the treatment of typhoid fever in Britain in 1964 are those of the prevention of relapse and of the chronic carrier state.

(B) THE INCIDENCE OF TYPHOID FEVER

The incidence of typhoid fever in Britain, before it was recognised as a separate entity, is difficult to assess, because of the multiplicity of descriptive terms used for continued fevers. It would appear that it was epidemic in Britain in the seventeenth century. Willis (1659) described three consecutive severe outbreaks in 1657 - 59, the second of which was influenza and the other two autumnal outbreaks of typhoid fever. He apparently had seen no similar disease before. However, typhoid had become endemic in certain areas, especially large cities, by the nineteenth century, presumably because of the number of unrecognised carriers. Perry (1836) stated that one in six cases of fever in Edinburgh had the intestinal lesions of typhoid. In 1873 Murchison said that "enteric fever.....is endemic in the British Isles, but is apparently most common in England, more common in Ireland than in Scotland, and in Scotland more common on the west than on the east coast." He tabulated the number of cases admitted to the London Fever Hospital and to Glasgow and Edinburgh Infirmaries from the first year in each place that it was distinguished from typhus in the records until 1870, and showed that there was little decrease in incidence in that time. These figures, shown in Table I, no doubt reflect only a small and variable proportion of the actual incidence. He also pointed/

TABLE I

CASES OF ENTERIC FEVER ADMITTED TO THE LONDON FEVER HOSPITAL GLASGOW ROYAL INFIRMARY AND EDINBURGH ROYAL INFIRMARY FROM THE TIME THEY WERE FIRST RECORDED UNTIL 1870

YEAR	LONDON FEVER HOSPITAL	GLASGOW ROYAL INFIRMARY	EDINBURGH ROYAL INFIRMARY
1847	?	127	
1848	152	7	
1849	138	?	
1850	137	?	
1851	234	44	
1852	140	134	
1853	212	45	
1854	228	92	
1855	217	145	
1856	149	163	
1857	214	157	
1858	180	117	
1859	176	87	
1860	95	91	41
1861	161	36	35
1862	220	79	79
1863	174	56	67
1864	253	40	140
1865	523	89 *	67
1866	582	68	69
1867	380	99	120
1868	459	224	104
1869	369	131	79
1870	595	105	69
TOTAL:	5,988	2,002	880

SOURCE: MURCHISON, C.(1873) "A TREATISE ON THE CONTINUED FEVERS OF GREAT BRITAIN" (IV) 442.

* * IN THIS AND THE SUBSEQUENT FOUR YEARS, THE ADMISSIONS INTO THE CITY OF GLASGOW FEVER HOSPITAL ARE INCLUDED WITH THOSE INTO THE ROYAL INFIRMARY.

pointed out that typhoid could still be epidemic in areas where it had been unknown for years, and he added that "these epidemics are local and circumscribed. Sometimes they are confined to a single house or village" - a clear indication that they were caused by carriers.

With the improvement in sanitation and water supplies which followed the Public Health Act of 1875, there was a marked fall in the incidence and mortality of typhoid fever, as evidenced by the annual death rates for Scotland and for England & Wales shown in Table 2. This decrease continued, until there were no deaths in 1950. Table 3 shows the five-year average incidence in Scotland since 1900. It is interesting to note that there were three marked decreases in incidence; the first, between 1905 and 1910, when the carrier state became recognised, and the other two during and after both World Wars. It seems reasonable to think that the last two were due to the large number of immunised ex-servicemen in the community.

After 1920 any occurrence of typhoid fever where more than one case was notified was called an outbreak; that is, typhoid fever is no longer considered endemic in any area of Britain. It is still, however, a common disease in many areas of the world, particularly in the/

TABLE 2

ANNUAL DEATH-RATES FROM TYPHOID PER 100,000 POPULATION

1870 - 1960

YEAR	DEATH RATES PER 100,000 POPULATION	
	ENGLAND & WALES	SCOTLAND
1870	38.8	35.9
1880	26.1	35.8
1890	17.9	19.3
1900	17.6	14.4
1910	4.2	5.5
1920	1.4	2.2
1930	0.8	0.5
1940	0.3	0.3
1950	0.0	0.0
1960	0.0	0.0

TABLE 3

FIVE-YEAR AVERAGE INCIDENCE OF TYPHOID FEVER IN SCOTLAND

5-YR. PERIOD	AVERAGE No. OF CASES	RATE PER 100,000 POPULATION
1900 - 04	3,987	89.2
1905 - 09	2,507	52.7
1910 - 14	1,469	30.9
1915 - 19	*	*
1920 - 24	611	12.5
1925 - 29	459	9.4
1930 - 34	448	9.3
1935 - 39	401	7.8
1940 - 44	106	2.1
1945 - 49	47	0.9
1950 - 54	17	0.3
1955 - 59	17	0.3
1960 - 64	82	1.6

* ACCURATE FIGURES NOT AVAILABLE.

the highly populated developing areas of Africa, Asia, South America and the Far East. The actual incidence is difficult to assess correctly, because of poor notification in many of these areas, as is shown by the unbelievably few notified cases in Africa and Asia in 1962 (Table 4). For example, the high incidence and particularly the death-rate which is recorded for the continent of America is a combination of the enormous incidence in South America and accurate reporting in North America, as may be seen from the selected breakdown of incidence shown in Table 5. This table shows the two countries in each continent which have the highest and the lowest incidence respectively. These figures also indicate that the high incidence in endemic areas does not give rise to natural immunity since the mortality is correspondingly high.

It used to be said that the incidence of typhoid fever was highest during and after the dry season. While this may still be true in areas with poor sanitation, in Britain at least an epidemic may occur at any time if any comestible becomes infected. There have been several major outbreaks in Britain in the last thirty years - one milk-borne (Bournemouth, 1936) one water-borne (Croydon, 1937) and one from ice-cream (Aberystwyth, 1946). The source of another outbreak in a hospital (Oswestry, 1948) was uncertain at the time that it occurred. There have, however, been several outbreaks in the last ten years, now known/

TABLE 4

WORLD INCIDENCE OF TYPHOID FEVER AND DEATH RATES

PER 100,000 POPULATION - 1962

COUNTRY	NUMBER OF CASES	CASES PER 100,000 POPULATION	DEATHS PER 100,000 POPULATION
AFRICA	35,545	1.19	0.03
AMERICA	44,929	11.09	0.56
ASIA	40,420	2.41	0.04
EUROPE	40,270	9.43	0.04
OCEANIA	407	2.47	0.01

SOURCE: WORLD HEALTH ORGANIZATION, EPIDEMIOLOGICAL & VITAL STATISTICS REPORT, 1962.

TABLE 5

INCIDENCE OF TYPHOID FEVER IN SELECTED COUNTRIES AND DEATH RATES PER 100,000 POPULATION - 1962

COUNTRY		NUMBER OF CASES	CASES PER 100,000 POPULATION	DEATHS PER 100,000 POPULATION
AFRICA	- U.A.R.	18,682 (P)	68.4 (P)	+
	NIGERIA	788 (P)	2.2 (P)	0.1
ASIA	- JORDAN	649	37.6	1.0
	JAPAN	910	1.0	0.0
AMERICA	- CHILE	3,688	46.1	2.9
	U.S.A.	608	0.3	0.0
OCEANIA	- TONGA	259	392.4	3.0
	AUSTRALIA	38	0.4	+
EUROPE	- ITALY	16,759	33.5	+
	NORWAY	2	0.1	-
	ENGLAND & WALES	130	0.3	0.0
	N. IRELAND	2	0.1	-
	EIRE	20	0.7	0.0
	SCOTLAND	13	0.3	-

SOURCE: WORLD HEALTH ORGANIZATION, EPIDEMIOLOGICAL AND VITAL STATISTICS REPORT, 1964, 17, 430.

(P) = INCLUDES PARATYPHOID

\+ = DATA NOT YET AVAILABLE -

\- = NIL OR MAGNITUDE NEGLIGIBLE.

known to have been caused by infected cans of meat (Pickering 1954, South Shields, Harlow and Bedford 1963, and Aberdeen 1964) and it is now presumed that this was also the source of the outbreak at Oswestry. These cans are believed to have been infected when unchlorinated water was used during the process of cooling. Thus modern techniques have brought with them new problems of public health and epidemiology.

(C) THE HISTORY OF TYPHOID FEVER IN ABERDEEN

Even before the manner of spread of disease was properly understood, Aberdeen led the field in Scotland in applying isolation and quarantine restrictions. Gibbets were sometimes used as early as the 15th century to enforce these measures, and Aberdeen suffered far less from plague than did other cities and large towns in Scotland (Ferguson, 1958).

In the first half of the nineteenth century "fever" was a deadly disease in Scotland. The first Registrar-General's detailed annual report, published in 1861, gave an analysis of causes of death in 1855; in this he found that the zymotic diseases were the chief cause of death, typhus fever being the most prevalent of this group.

There were three severe outbreaks of "fever" in Britain in the nineteenth century before 1840, and these affected Aberdeen no less than elsewhere. The worst of these was from 1835 to 1839. The number of cases treated in hospital in Aberdeen in these five years is shown in Table 6, and this was no doubt only a small part of the actual incidence. It is probable that in Aberdeen, as was observed by Perry in Edinburgh and Lombard in Dublin most of these cases/

TABLE 6

CASES OF "FEVER" ADMITTED TO HOSPITAL

ABERDEEN, 1835 - 39

YEAR	NUMBER OF CASES	NUMBER OF DEATHS
1835	616	24
1836	684	42
1837	1,307	76
1838	1,272	44
1839	1,308	85

SOURCE: FERGUSON, T. (1958) "SCOTTISH SOCIAL WELFARE 1864-1914" EDINBURGH & LONDON

cases were typhus, but a few were typhoid fever.

Drainage - Until the 1860's the general public regarded fever as an act of God, to be accepted with resignation, but there then began a reformation in sanitation and hygiene throughout Scotland, and 1867 brought the first Public Health (Scotland) Act, a summation of Public Health and Sanitary Acts already existing in England & Wales. Water supplies in Aberdeen had been extended and replanned in 1866, and from 1867 onwards a larger and more thorough system of drainage was adopted. In 1869 Colonel Henry Erskine made a contract with the Town Council to establish the first "sewage farm" in the North-East by utilising part of the City's sewage. The next few years saw further extension to water supplies and ventilation of the sewers, and in 1879 Aberdeen's Sanitary Department became a separate entity. One of its first actions was to institute in 1880 a system of daily cleansing, and to abolish ash-pits and privies; in this it was ten years ahead of Glasgow and Dundee.

In 1895 four large sewage farms were brought into operation in the Deeside area of Aberdeenshire, thus greatly decreasing the pollution of Aberdeen's water supply, which came from that area. Two further sewage farms were completed in 1906 and by 1912 most of the large houses on Deeside also had new drainage laid to prevent crude sewage from flowing into the River Dee.

PUBLIC/

(i) PUBLIC HEALTH

The reporting of infectious diseases was initiated in 1881. In 1882 the Medical Officer of Health of Aberdeen, Dr. W.H. Simpson, in a paper read to the Aberdeen Philosophical Society, summarised the health of Aberdeen in the previous twenty-five years. He said "good drainage has had a most wonderful effect, especially on two diseases, viz. Typhoid fever and Phthisis: in one case by preventing contamination of the soil, in the other by drying the soil", and he observed that most cities in Britain and in Europe had reached the same conclusion. Certainly the number of deaths from the fevers in Aberdeen during 1870-81 was 582, as opposed to 1,277 in the preceding twelve years - "a great and steady decline" (Simpson).

With each successive epidemic in the 19th century, more beds were added to Aberdeen Royal Infirmary, first opened in 1742, and in 1844 a fever house was established; but this was not nearly enough, and in 1875 a special hospital for infectious diseases was built. This same hospital coped with the majority of typhoid patients in the 1964 outbreak.

Thus, in the latter half of the 19th century, steady progress was made towards a cohesive Public Health and hospital system. There had been an "Officer of Health" in Aberdeen since 1862, but in 1881 this was combined with the posts of Police Surgeon, Fever Hospital Superintendent and other part-time appointments under the/

the title of Medical Officer of Health. In 1896 the Medical Officer of Health of Aberdeen County, Dr. J. P. Watt, proposed a central bacteriology service for the use of both Local Authorities and medical practitioners in the area. The proposal was adopted, and the scheme flourished and served all of the North-East of Scotland until the introduction of Regional Hospital Board Areas in 1948.

(ii) THE INCIDENCE OF TYPHOID FEVER IN ABERDEEN IN THE 20th CENTURY

The incidence of typhoid fever in the City of Aberdeen, as in other areas of Britain, fell remarkably in the early years of the 20th century, as can be seen in Figures 1 (a) and 1 (b).

At the turn of the century the incidence in the City was relatively high: from 1898-1901 inclusive the annual average was 147 cases. There was a coincidental rise in cases in Deeside at the beginning of this period, due to infected milk at Aboyne, and no doubt there was some pollution of the city water supply despite the irrigation farms. Many cases in various parts of Aberdeen were due to infected milk supplies, but the Medical Officer of Health also noted that, of 113 cases notified between November 1900 and March 1901, none could definitely be traced to either milk or water, and that the incidence was evenly spread over these months, but occurred in only a few districts of Aberdeen. (M.O.H. Report, 1901).

Unfortunately/

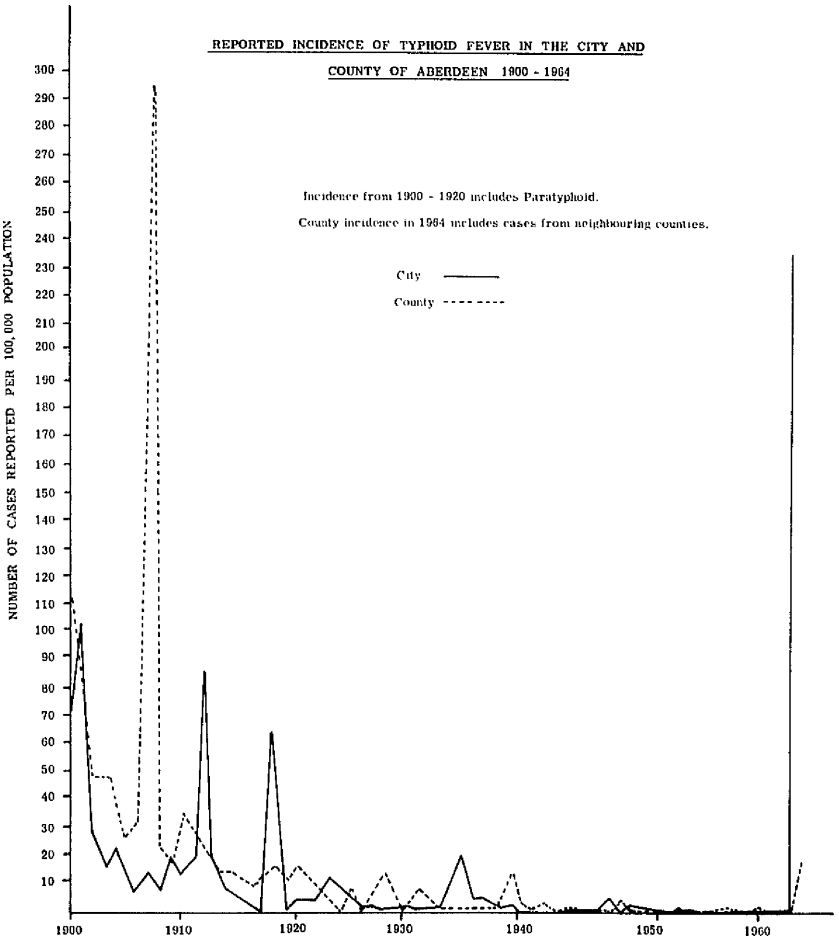


Fig. 1a - Reported incidence of Typhoid Fever in the City and County of Aberdeen 1900 - 64.

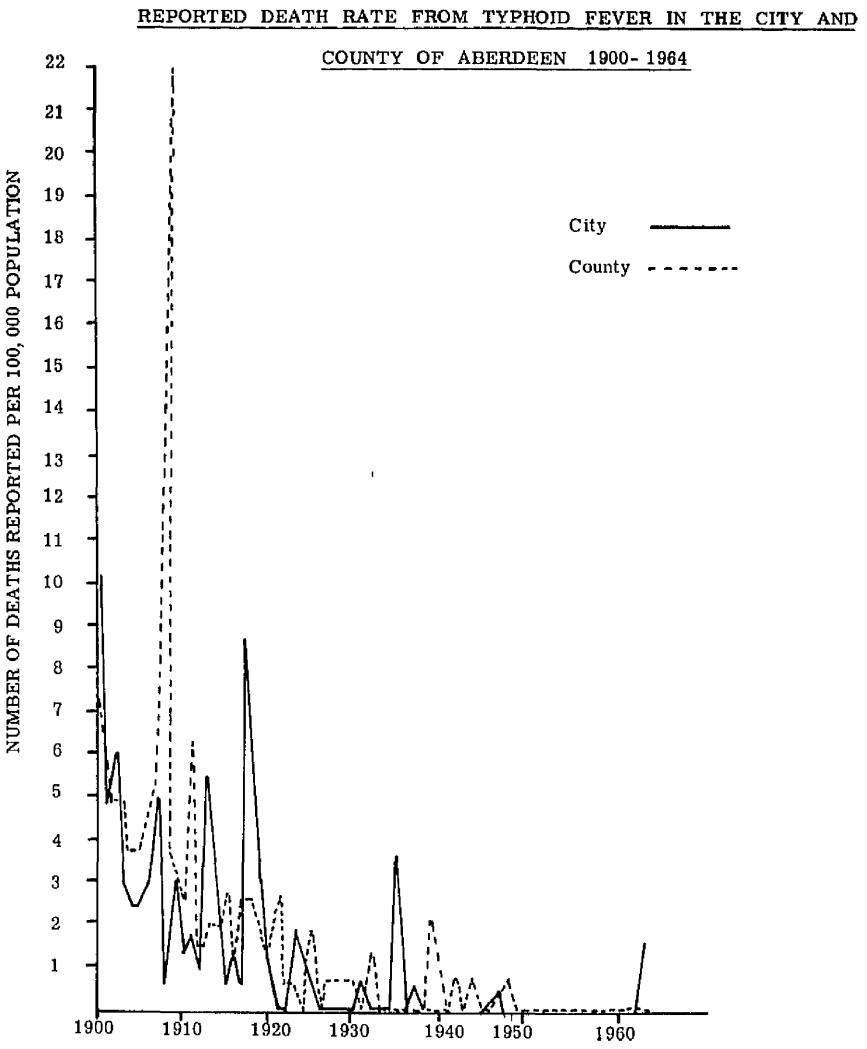


Fig. 1b - Reported death rate from Typhoid Fever in the City and County of Aberdeen 1900 - 64.

Unfortunately he attributed this to "heightened susceptibility in the presence of infecting cases", and not, as would no doubt have been correct, to the production of many carriers in the previous two years.

There were three epidemics in Aberdeen City in the first half of the century which are worthy of mention. The first, in 1912, was presumed to be milk-borne, although the Medical Officer of Health made a good case form a water-borne infection due to a drain bursting into the River Dee some miles from Aberdeen (Hay,1912). Investigations of the first cases suggested that a creamery which had supplied several milk dealers might be the common source, and three days after the beginning of the outbreak this creamery undertook to sterilise all milk issued. Further enquiry led to one particular farm which supplied the creamery and another dairy; the farmer's mother had had typhoid fifty years previously, but after one negative stool specimen at this time she refused further examination. Then it was discovered that a probable case of typhoid fever, who had not had faeces specimens examined, had been in Aboyne Hospital, Deeside, for two months before the beginning of the outbreak. One month before the outbreak a drain between the hospital and the sewage farm had burst, and sewage from the hospital had overspilled into the River Dee at a point nine miles above the city water reservoir. A

lengthy/

TABLE 7

SOME COMPARISONS BETWEEN OUTBREAKS OF TYPHOID FEVER IN 1935 AND 1964

FACTORS COMPARED	1935	1964
NUMBER OF PATIENTS PER HOUSEHOLD	2.2	1.5
PERCENTAGE OF SECONDARY CASES	28.0	0.0
RELAPSE RATE	20.5	18.3
MORTALITY RATE	17.1	0.6
MEAN DURATION OF STAY IN HOSPITAL	50.0	38.6

lengthy agrument followed between the Medical Officers of Health of Aberdeen City and County as to whether it was a milk-borne outbreak from the farmer's mother in Aberdeen or a water-borne outbreak from the patient in Aboyne. Neither source was ever proved, but the consensus of opinion was that the outbreak was milk-borne. The fact that most patients were aged 5 - 25 years would tend to support this view.

A total of 101 cases was involved, of whom 97 were hospitalised. The mortality was 10 cases. It is interesting to note that there was a small concurrent outbreak of paratyphoid fever, totalling 13 cases; 2 patients suffered from both diseases with a short interval between. Several typhoid cases were treated with typhoid vaccine, which appeared to reduce the temperature and shorten the febrile illness.

A second large outbreak occurred in 1918 when a dairy farmer's wife caused a milk-borne outbreak affecting 97 persons, of whom 14 died (14.4%). All these cases were admitted to hospital, where bacteriological examination showed in about half of them a mixed infection with B. typhosus and B paratyphosus B. The farmer's wife was removed to hospital in the fifth week of the outbreak, but a further 30 cases occurred. During this outbreak prophylactic inoculation of 72 contacts in infected households was performed/

performed, and none of them developed typhoid fever. However, none of them was exposed to infection after being immunised, and their freedom from illness should not necessarily be attributed to the effect of the vaccine.

The third outbreak of typhoid fever to be mentioned occurred in 1935 when there were 39 cases, of whom 6 died. The source of infection was a small shop where a woman had been ill for several weeks; 26 of the patients had eaten cooked tripe or "potted head" bought from there. When the members of this household were tested as contacts, the woman's brother was found to be excreting S. typhi in faeces and urine. He had a history of gastric trouble during the previous seven years, and was removed to hospital for observation and treatment as a possible chronic carrier. However, four days later he developed severe typhoid fever and died on the 61st day of illness. It is probable that the positive specimens were obtained during the incubation period, rather than that he was a chronic typhoid carrier. This outbreak was well documented by Dr. D. Bell (1937) and some interesting comparisons may be made with the 1964 outbreak. It was one of the first outbreaks known to be due to infected cold cooked meats and the quantity of food initially infected was probably much more than the six pounds of corned beef incriminated in the 1964 outbreak. Yet modern sales techniques/

techniques of supermarkets and slicing-machines resulted in 469 proved cases in 1964, as opposed to 39 in 1935. Other comparisons are shown in Table 7.

There were 3 faecal carriers detected as a result of the outbreak, 2 of whom were cured by cholecystectomy. The third carrier was the woman who first became ill, and she was also a urinary carrier; urine specimens remained positive after cholecystectomy and she died following nephrectomy.

During this outbreak Dr. D. Bell conducted a controlled trial of Lister Institute antityphoid serum in the treatment of typhoid fever. There was great interest at that time in evolving a serum suitable for treating typhoid and Felix, among others, had reported promising results with the Lister Institute serum, which contained 'O' and Vi antibodies (Felix 1935). However, Dr. Bell, with 19 cases and 20 controls, found it to be of no value in reducing fever and indeed to be at times dangerous when given intravenously, as was recommended by the manufacturers (Bell 1937).

From 1935 until 1964 the City of Aberdeen was remarkably free from typhoid fever. No cases and no carriers were notified in Aberdeen between 1953 and 1964, although there were some cases in the surrounding districts.

(iii)/

(iii) THE INCIDENCE OF TYPHOID FEVER IN ABERDEEN COUNTY

Aberdeen being the focal point of, and the main shopping centre for, the North-East of Scotland, it is advisable to consider also the incidence of typhoid fever in the counties of Aberdeen and Kincardine. At the turn of the century there were frequent sporadic outbreaks in both counties, and typhoid fever appeared to be endemic in a number of farms; Ferguson (1958) attributed this to the periodic emptying of the farm midden.

In 1907 in Peterhead there occurred a prolonged and widespread outbreak involving 423 cases over a period of four months, the largest recorded epidemic of typhoid fever in the North-East before 1964. Such was its extent that the immediate conclusion reached was that it was water-borne, especially since several of the town wells and burns were found to be highly polluted with faecal contaminants, although no typhoid bacilli were found. Further investigations revealed, however, that the same milkman supplied 87% of the cases who took ill in the first two weeks, and it was finally established that the source was the mother of a maid-servant at the milkman's farm. The girl had nursed her family during an undiagnosed illness six months previously, and although herself never ill, had transported the germ back to the farm. Two weeks later the mother was found to have S.typhi in her urine, although not in her stools - probably the first urinary carrier identified in Scotland. (Hay 1908).

The Medical Officer of Health of Aberdeen City, Dr. Matthew Hay, compared/

YEAR	CITY OF ABERDEEN			COUNTIES OF ABERDEEN AND KINCARDINE			
	No. OF CASES	PHAGE TYPE	REMARKS	No. OF CASES	LOCATION	PHAGE TYPE	REMARKS
1935	39		WOODSIDE OUTBREAK	-			
1936	-			1 1	NEAR TURRIFF OLDMELDRUM		CHILD. (GRANDMOTHER KNOWN CARRIER) BECAME A CARRIER (SEE CITY 1945)
1937	4		MEMBERS OF CYCLING CLUB WITH 51 MEMBERS ONE DIED.	1 1	INVERURIE DELLAVAIRD		ADULT MALE. ADULT MALE.
1938	-			-			
1939	1	L.2	GIRL, BRIDGE OF DEE	8 12 1 1	OLD DEER PETERHEAD DELLAVAIRD OLDMELDRUM		CARRIER FROM 1919. 2 DIED; CARRIER SUSPECTED, NOT PROVEN. ADULT MALE (DIED). SOURCE: SAME WOMAN WHO CAUSED CASE IN 1937; SHE HAD HAD TYPHOID 40 YEARS PREVIOUSLY IN DEVON. BROTHER-IN-LAW OF CASE IN 1936; CARRIER WAS THE MOTHER (TYPHOID 1917), WHO THEN BECAME NEGATIVE IN 1949.
1940	-			1	FRASERBURGH		DIED
1941	-			1	STRATHDON		ADULT FEMALE, PREVIOUSLY HAD TYPHOID IN RUSSIA 1916. PUS FROM BONE ABSCESS GREW S. TYPHI. (IMPERFECT VI)
1942	-			3 1	MAUD BALLATER	A C	MEMBERS OF ONE FAMILY (ONE DIED) ADULT MALE FROM ARMY CAMP
1943	-			-			
1944	1	E.1	CHILD WHO HAD BEEN CAMPING AT TARLAND	1	FRASERBURGH	E	CHILD AGED 6 (AT LIGHTHOUSE)
1945	1 2	A J	CHILD, GRANDDAUGHTER OF OLDMELDRUM PATIENT (SEE 1936) ADULT MALES, HOME FROM ABROAD; ONE DIED.	-			
1946	1	E	ADULT MALE	1	INVERURIE	E.1	ADULT MALE
1947	6 1	A UNTYPE-ABLE	ADULT FEMALES IN ROYAL MENTAL HOSPITAL ONE DIED. SOURCE: A PATIENT WHO WAS FINALLY CLEARED IN 1953. ADULT MALE, GORDON BARRCKS, FROM HOLLAND	-			
1948	1	E	IN GARTHDEE; APPENDICECTOMY PERFORMED.	3 4	WOODCOTE, STONEHAVEN, FRASERBURGH	E.1 A	IN GERIATRIC UNIT; CAUSE: CARRIER FROM INSCH, AGED 94, WHO DIED. ONE CASE BECAME A CARRIER AND DIED IN AN ISOLATION UNIT IN 1952. SOURCE: CARRIER WHO HAD TYPHOID IN GLASGOW IN 1915. SHE DIED LATER.

1949/

YEAR	CITY OF ABERDEEN			COUNTIES OF ABERDEEN AND KINCARDINE			
	No. OF CASES	PHAGE TYPE	REMARKS	No. OF CASES	LOCATION	PHAGE TYPE	REMARKS
1949	2	E.1	IN ROYAL MENTAL HOSPITAL; ONE WAS A CARRIER AND THE OTHER BECAME SO; BOTH ARE STILL IN AN ISOLATION UNIT.	-			
1950	1 1	E.1 E.1	IN GARTHDEE - CHILD IN ST. CLEMENTS - ADULT FEMALE	-			
1951	-			-			
1952	1		ADULT MALE - SOURCE UNKNOWN; UNTYPEABLE	-			
1953	1	E.1	CHILD - CENTRAL ABERDEEN	-			
1954	-			2	NEAR ABERDEEN	E	CHILDREN WHOSE GRANDMOTHER HAD TYPHOID IN INDIA 30 YEARS PREVIOUSLY. SHE BECAME NEGATIVE IN 1955.
1955	-			-			
1956	1		ADULT MALE HOME FROM HOLIDAY IN IRELAND; UNTYPEABLE.	-			
1957	-			1	PETERHEAD	F.1	GIRL.
1958	-			1	PETERHEAD	F.1	ADULT FEMALE, GRANDMOTHER OF 1957 CASE IN PETERHEAD (DIED).
1959	-			-			
1960	-			2	PETERHEAD	F.1	ADULT FEMALES; FRIENDS OF 1957 CASE, ONE STILL CARRIER IN 1961.
1961	-			-			
1962	-			-			
1963	-			-			

compared this outbreak in Peterhead with the one in the City in 1912, and pointed out that, although both started with the same number of cases in the first two weeks, lack of isolation facilities in Peterhead had been largely responsible for the enormous difference in the extent of the two outbreaks. (Hay 1912).

Dr. J.P. Watt, Medical Officer of Health for Aberdeen County at that time, was concerned about the problem of typhoid carriers, and in 1918 he wrote to all Medical Officers of Health in England and Scotland, asking for information about known carriers between 1908 and 1918. There were surprisingly few in Scotland; he himself had discovered 20 in Aberdeenshire during this period, but only 11 more were on record in the rest of Scotland. Of these 11, 4 were in Banffshire, where Dr. A. Lodingham, Medical Officer of Health, was also known for his great interest in typhoid carriers. The figures which Dr. Watt received for England and Wales, excluding London, showed a fall from 5,322 in 1908 to 1,465 in 1918. (Taken from the records of Aberdeen County Health Department).

The largest outbreak in the county of Aberdeen after 1907 was one of 25 cases in 1920, when 2 more carriers were identified. In 1929 there was an outbreak of 17 cases in an outlying area, when once again a carrier was found. As can be seen from Figure 1 (a), cases apart from these outbreaks were sporadic.

Despite the much-used road and rail communications between Aberdeen and/

and its surrounding districts, there has been little connection between the town and country incidence of typhoid fever in the last thirty years. The incidence of typhoid in Aberdeen, Kincardineshire and Aberdeenshire since 1935 is detailed in Table 9. The information is derived from records at the Regional Laboratory, City Hospital, Aberdeen. The most recent cases, namely those in Peterhead since 1957, are all apparently connected. Unfortunately the woman who became ill in 1958 died before it was possible to ascertain whether she was a carrier from the 1939 outbreak and, since the latter outbreak just preceded the discovery of 'phage-typing, no connection could be established by that method. The one patient who was still a carrier in 1961 has not been tested since, but no more cases have been reported from Peterhead.

At the present time there are only two known carriers in the North-East of Scotland other than those arising from the outbreak in 1964. (Medical Officers of Health, 1965). One is a woman who had typhoid fever in Russia more than twenty years ago. In 1963 a woman from England who had been visiting this person developed typhoid fever, 'phage-type N, and a specimen of stool from the Russian yielded S. typhi of the same 'phage type, and she is still known to be excreting bacilli. The other is a man who recently came to this area, and who has been a known carrier of S.typhi 'phage type T for some twenty years. He was discovered when he infected his son, but although still excreting bacilli/

bacilli has not given rise to any further known cases of typhoid fever.

This, then, was the known position as regards typhoid fever and typhoid carriers in Aberdeen and suzrounding district early in 1964.

1936 -1963

INCIDENCE OF TYPHOID FEVER IN ABERDEEN DISTRICT

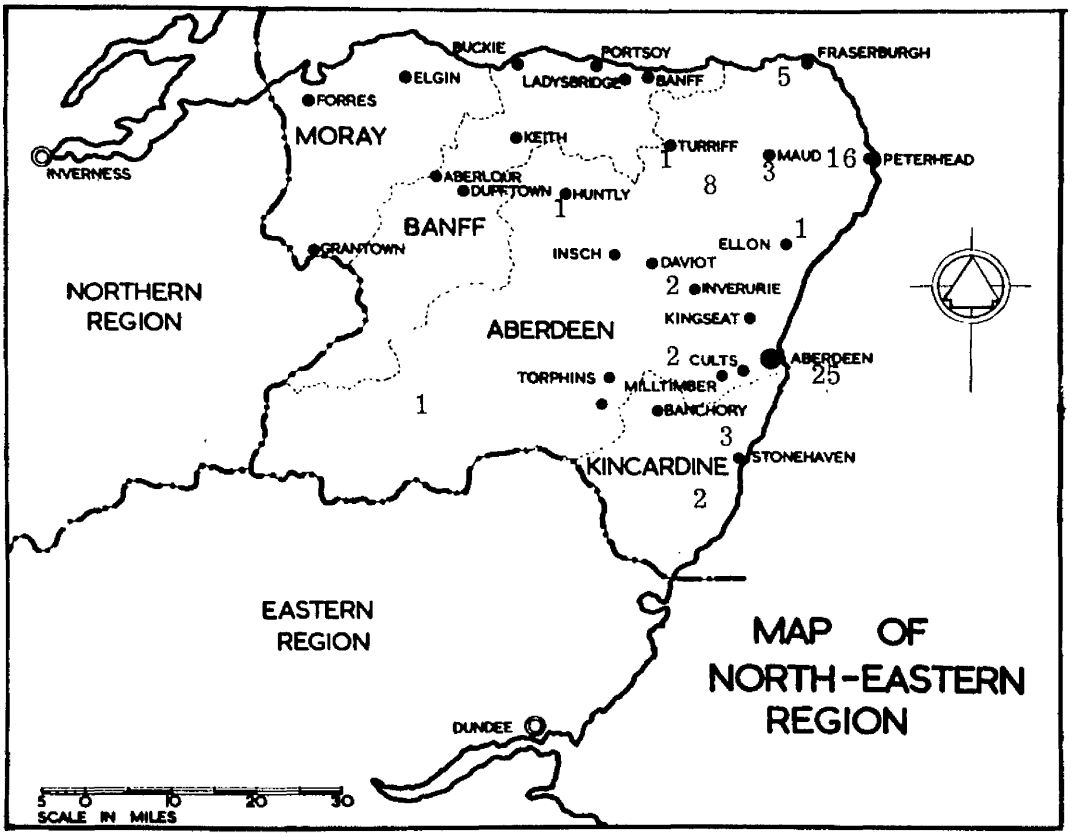


Fig. 2 - Incidence of Typhoid Fever in Aberdeen and district 1936 - 63

(D) THE PATHOGENESIS OF TYPHOID FEVER

(i) THE ROUTE OF SPREAD OF INFECTION

Besredka in 1927 said, "no matter what the portal of entry of the virus may be - whether oral, intramuscular, intravenous, of subconjunctival - the organ that enters in reaction with it is always the same. The virus invariably travels towards the intestine".

Typhoid fever, like all Salmonella infections, is acquired naturally by the ingestion of the organism, although it has been produced experimentally by the subconjunctival route (Sedan and Hermann, 1924). Neter (1950) found Salmonellae in the nasopharynx and throat of two infected children, but his suggestion that such infections could be airborne has received no support. Von Drigalski (1904) found that 40% of cases in one outbreak had faucial inflammation and he cultured *S.typhi* from the tonsils of many of these cases, but it is generally believed that the majority of bacilli enter the host via the intestinal lymphatics (Wilson and Miles, 1965).

Orskov and his co-workers (1928-1932) did a great deal of experimental work to ascertain the exact route of spread of infection from the intestine. This was summarised by Madsen in 1937, who presented it clearly in diagrammatic form, as shown in Figures 3(a) and 3(b)./

3 (b).

In the experiments of Orskov and his co-workers, a number of mice were fed with Gaertner bacilli at the same time and killed at intervals, in order to determine the mode of spread of infection from the time of ingestion to the time of excretion. The results showed that the first sites of bacteria outside the intestinal canal were simultaneously the submaxillary and mesenteric lymph glands. Thereafter it took two days in mice for the organisms to reach blood, liver or spleen. This primary bacteraemia was short-:lived. Madsen stated that "only relatively few bacteria enter the blood stream in the early phase of the bacteraemia and they are quickly removed from the blood by the fixed phagocytes, especially in the liver and spleen, to a lesser degree in the peripheral lymph glands". The experiments showed that the bacteria multiplied within these organs and after several days were also found in the blood stream, this time in large numbers.

Further experiments with mice fed with B. aertrycke showed that a few bacteria were found in the intestine in the first twenty-:four hours after infection, none from the third to sixth days, and increasing numbers thereafter. The upper sections of the intestine were invariably the first to become infected. These experiments were/

were repeated with other bacilli, including S. typhi, and the findings were the same. Madsen stated that "it seems reasonable to think that the bile passages play an essential role in the secondary appearance of the microbes in the intestine, even when the infection takes place by way of the mouth".

The consensus of opinion to-day is that this is indeed the mechanism of spread of infection within the body of the host, that is that typhoid fever is primarily a bacteraemia. From the blood the bacteria spread to other organs, then return to the blood stream and thence to the gut via the biliary system. It is thought that the incubation period corresponds to the phase preceding the secondary invasion of the blood stream and intestine from the sites of proliferation in liver, spleen and lymphatic glands. (Wilson and Miles, 1965).

Orskov also noted that with all bacteria there were some cases where infection did not spread beyond the regional lymph glands. Madsen's theory was that there is a blockade at these glands; if it is overcome the infection passes to the blood stream to become generalised, but if the blockade is permanent then the infection remains localised. He was uncertain as to the nature of the blockade, but regarded it as part of the natural defence mechanism. It is now believed that this is so, and that the first stage of the fight against infection/

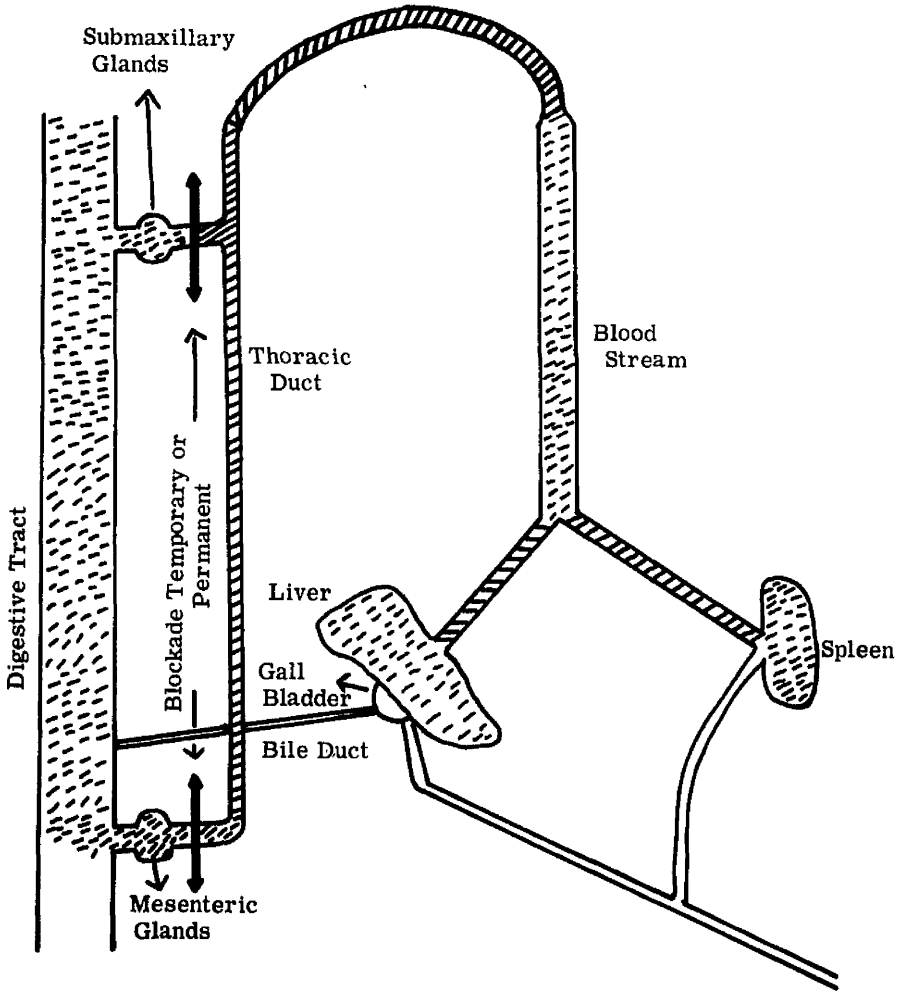


Fig. 3a - The route of spread of typhoid infection within a host - route of invasion of the blood stream by bacteria.

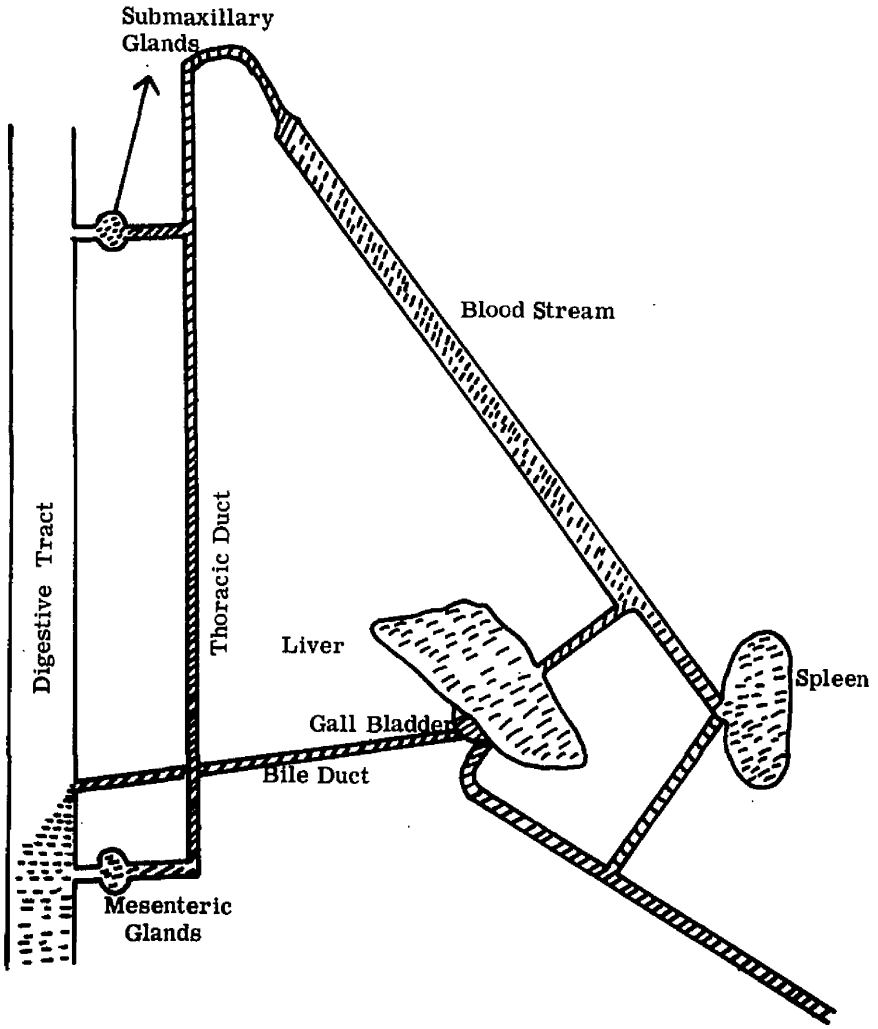


Fig. 3b - The route of spread of typhoid infection within a host - the subsequent re-excretion of bacteria.

infection takes place at the lymphoid tissues nearest to the site of entry of bacteria, in a manner which will be described later. The regional lymph glands are the first major aggregation of lymphoid tissue which bacteria encounter during their invasion of the host.

(ii) THE ROLE OF ENDOTOXIN

It is thought that the symptoms of typhoid fever are produced by the release of endotoxin from the bacteria, although the evidence at present available is largely circumstantial. Favorite and Morgan (1942) produced typical symptoms in man by the intravenous injection of endotoxin, and Morgan (1948) then showed that tolerance to endotoxin could rapidly be induced by giving daily injections of endotoxin. He also found that tolerance to endotoxin was present during convalescence from typhoid fever and persisted for variable periods up to six months from the time of infection (Neva and Morgan, 1950). The latter finding was confirmed by Greisman et al.(1963); during their studies two patients,with induced typhoid bacteraemia which was asymptomatic, did not develop tolerance to endotoxin (Snyder et al, 1964), which suggested that the presence of symptoms was essential for the production of tolerance. The action of endotoxin-producing symptoms is, however, non-specific; for example, the same symptoms are produced by endotoxin to E. coli as to S. typhi.

(iii)/

(iii) THE MECHANISM OF RESISTANCE TO INFECTION

In general terms the extent of any infection in a host depends on the balance of the host-parasite relationship. If the host is stronger, the organism will either be refused entry or be overcome inside the host and "normal" health restored. If the parasite is stronger, the host will be either temporarily or permanently over-run and illness or death ensue.

There are two main lines of defence against infection within a host. These are:

(1) the removal of bacteria from blood and tissues by cells which have the power to ingest them.

These cells are called phagocytes ("eating cells") (Metchnikoff, 1887).

(2) the bacteriostatic and bacteriocidal components of body fluids.

The most important of these humoral elements in typhoid fever is the specific antibody which is produced in the presence of the bacterial antigens of S. typhi. (Von Behring and Kitasato, 1890).

(1) There are two main types of phagocytic cell. The first of these to take part in resistance to infection is the mobile or "wandering" cell which moves to the initial site of infection in the/

(1) Contd.

the tissues. These cells may be polymorphonuclear leucocytes or large mononuclear leucocytes, often called "macrophages". In addition to these mobile cells, there are fixed phagocytic cells which are found mainly in the endothelium of the sinusoids of various organs such as liver, spleen, bone-marrow and lymph nodes. These cells constitute the reticulo-endothelial system (Aschoff, 1924). It has also been shown that other cells, for example centrilobular liver cells, may act as phagocytes if a large quantity of foreign material is introduced into the body (Lison and Smulders, 1948).

When the bacterium is taken up by the phagocytic cell it is temporarily devitalised (Olitzi et al, 1964). One of three things may then happen:-

(a) the bacterium is killed and digested by the phagocyte
(b) it remains static within the phagocyte
(c) it multiplies within the phagocyte after a period of rest, and may either overpower it and be released or remain within the cell until it dies naturally and is broken up.

Wilson (1953) demonstrated a fourth outcome, namely that the phagocytes may eject viable bacteria and themselves remain viable. Suter (1956) in a review of the phagocyte-pathogen relationship described it thus:-

"The/

"The interaction between phagocytes and pathogens..... includes migration, phagocytosis and attempts at intracellular digestion. Any deviation from this basic pattern must be explained by the peculiarities of the pathogen, the phagocyte, or the environment in which the interaction takes place. Environmental influences can be non-specific or specific, and affect the viability of the pathogen or its ingestion. The resistance of the pathogen to the intracellular environment determines its fate after it has been ingested ".

Suter described three variations of phagocyte-pathogen relationship which depend on which environment the bacterium prefers. Thus, obligate extra-cellular pathogens cannot survive intracellularly whereas obligate intracellular pathogens cannot survive extra-cellularly. He stated that S. typhi was a facultative intracellular parasite, that is, it may survive or proliferate either extra or intracellularly. This was first demonstrated by Goodpasture in 1937, when he found typhoid bacilli within plasma cells in intestinal lymphoid tissue.

Some of the factors which influence the phagocyte-pathogen relationship have been demonstrated in laboratory animals. A virulent strain of S. typhi was shown to survive intracellularly within phagocytes where an avirulent organism was easily destroyed (Olitzki et al. 1964) Oakberg/

Oakberg (1946) demonstrated genetic differences in the ability of phagocytic cells to digest the organism. More recently in Adelaide, South Australia, workers have shown *in vivo* that macrophages are heterogeneous in respect of their ability to kill bacteria once they are within the macrophage, and that this heterogeneity is due to the presence of some incompetent macrophages (Jenkin, Rowley and Auzins, 1964). Environmental differences, such as body temperature, have been shown to affect phagocytosis (Bell, 1949).

(2) Antibody is a specific environmental factor which affects the phagocyte-pathogen relationship. The site of antibody production depends on the route of infection: in oral infection the lymph glands of the intestine are the first site of antibody production, whereas the spleen, lung, and bone-marrow are the first places where antibody is found after intravenous infection (Doan, 1940). It is thought that antibody is formed in the plasma cells of lymphoid tissue, the bacterial antigen being taken up by the cells from the tissue fluid (Coons *et al*, 1955). The presence of humoral antibody, whether produced by infection or by immunisation, is largely responsible for immunity to subsequent infection. When the bacterium comes in contact with antibody the latter agglutinates its own antigen in the bacterium, surface antigens being the first to be agglutinated.

As/

As early as 1916 Rous and Jones showed that intracellular organisms were protected from the action of humoral antibody. Jenkin and Rowley (1963) have further demonstrated in mouse experiments that the presence of humoral antibody increases not only the rate of uptake of bacteria by phagocytic cells but also the ability of these cells to destroy the bacteria once the latter have been ingested. If both these findings are correct, humoral antibody must act by sensitising the bacteria both to ingestion and to killing by the phagocytic cells.

Jenkin, Rowley and co-workers have also studied the theory of cellular as opposed to humoral immunity. This idea was first propounded by Lurie in 1942, when he observed that mononuclear phagocytes of immunised animals inhibited the multiplication of bacteria in the absence of immune body fluids. Rowley, Turner and Jenkin (1964) showed that immunity to infection with S.typhimurium in mice could be transferred either with cells or with serum, and suggested that acquired cellular immunity to infection is due to the presence of cell-bound antibody. If this concept is correct, then the measurement of immunity by serum antibody assays is in no way a true indication of the level of immunity in the tissues.

This/

This, then, is a brief outline of the state of our present knowledge about typhoid fever. Many problems remain to be solved with regard to the prophylaxis and treatment of typhoid fever, and the precise reaction between host and pathogen is not yet completely understood, nor the effect of chemotherapy on this reaction.

In the subsequent sections of this thesis, an attempt is made to elucidate some aspects of these problems.

SECTION II

THE OUTBREAK OF TYPHOID FEVER IN ABERDEEN IN 1964

This section describes the epidemiology of the outbreak of typhoid fever in Aberdeen in 1964 from the time that the first case was admitted to hospital. The control of the admission of patients to hospital is discussed, and the criteria for "clearance" are outlined. The typhoid patients are described with regard to their age, sex and social background, and some clinical features and complications are noted. In particular, the effect of the severity of the initial infection on the subsequent course of the disease is examined.

SECTION II

A. SOURCE OF DATA

The information on which the following account is based is derived from two main sources: hospital records and epidemiological summary sheets designed for the outbreak. Data from these were cross-checked and doubtful points were clarified by patients at the follow-up clinics. General practitioners willingly provided any further information required. Any discrepancy between data given here and in the Report of the Departmental Committee of Enquiry (1964) is due to corrections made by patients at the later clinics.

Method of Working

The Chi-Square test with Yates' correction was used for most calculations, which are to be found in the appendices. Expected numbers are shown in brackets. Where numbers were too small or were unsuitable for the chi-square test, the fourfold table test, using the hypergeometric distribution or a comparison of proportions, was applied instead.

The t-test was used to measure differences between means.

Significant levels of differences were interpreted, as follows:-

$P < 0.05$	- "possibly significant"
$P < 0.01$	- "significant"
$P < 0.001$ or less	- "highly" or "very significant".

Where the probability of the difference occurring was greater than 0.05 (1 in 20), chance was taken to be the more likely explanation and the difference was considered "not significant".

Only calculations which showed a significant difference are included in the appendixes, unless a non-significant distribution was considered to be pertinent.

B. THE CAUSE OF THE OUTBREAK

On May 19th, 1964, an agglutination titre to S.typhi 'H' of 1:5120 was obtained from the serum of a student who was ill in Aberdeen Royal Infirmary. This was followed the next day by the isolation of S. typhi from the blood of this and one other patient, also a student, in the Infirmary and of two housewives who were patients in the City Hospital, Aberdeen. By the evening of 22nd May there were 13 confirmed and 5 probable cases of typhoid fever

in hospital, from 5 households. As the number of admissions increased so did the dispersion of cases until all areas of the city were affected. Between 16th May and 31st July, 540 patients were admitted to hospital suspected of having typhoid fever and 4 further cases remained at home. Of these 540 patients, 37 did not have typhoid fever and a further 38 did not have the diagnosis satisfactorily confirmed; that is, there were 469 proved cases of typhoid fever.

The outbreak was caused by S. typhi 'phage-type 34. At the time of the outbreak this strain was thought to have occurred in Britain only once before, in a woman in Greenock in 1955 who ate dulse sent to her from Northern Ireland. Subsequently, however, Dr. E. S. Anderson of the Central Enteric Reference Laboratory at Colindale re-examined the organism which had caused a hospital outbreak at Oswestry in 1948 and discovered that this was, in fact, also 'phage-type 34. The first positive isolation from all patients in Aberdeen was sent to the Enteric Reference Laboratory for 'phage-typing. All but 6 of these were S. typhi 'phage-type 34. The remaining 6 were 'phage-type A, which is the parent 'phage-type: it is believed that these 6 had reverted from 'phage-type 34. (Milne Report, 1964).

In an account of the previous outbreak at Oswestry in 1948, Felix and Anderson (1951) commented on several unusual features. These were:

(1) a high incidence of symptomless excreters and "precocious carriers".

(2) long incubation periods.

(3) a low case-fatality rate.

(4) a low incidence of the chronic carrier state.

It will be shown later that there was a certain similarity between the incidence of these features in Oswestry and in Aberdeen.

The original vehicle of infection, namely a can of corned-beef imported from South America, has been discussed at some length in the Report of the Departmental Committee of Enquiry (1964), headed by Sir David Milne. All the available evidence, albeit circumstantial, pointed to the infection of the can during cooling with unchlorinated river-water in South America. It also indicated that the infection was spread from one cold meat to another by the machine which was used to slice all cold meats sold in the shop concerned. As a result of this Report, food-hygiene regulations were re-examined and food-canning processes were carefully studied.

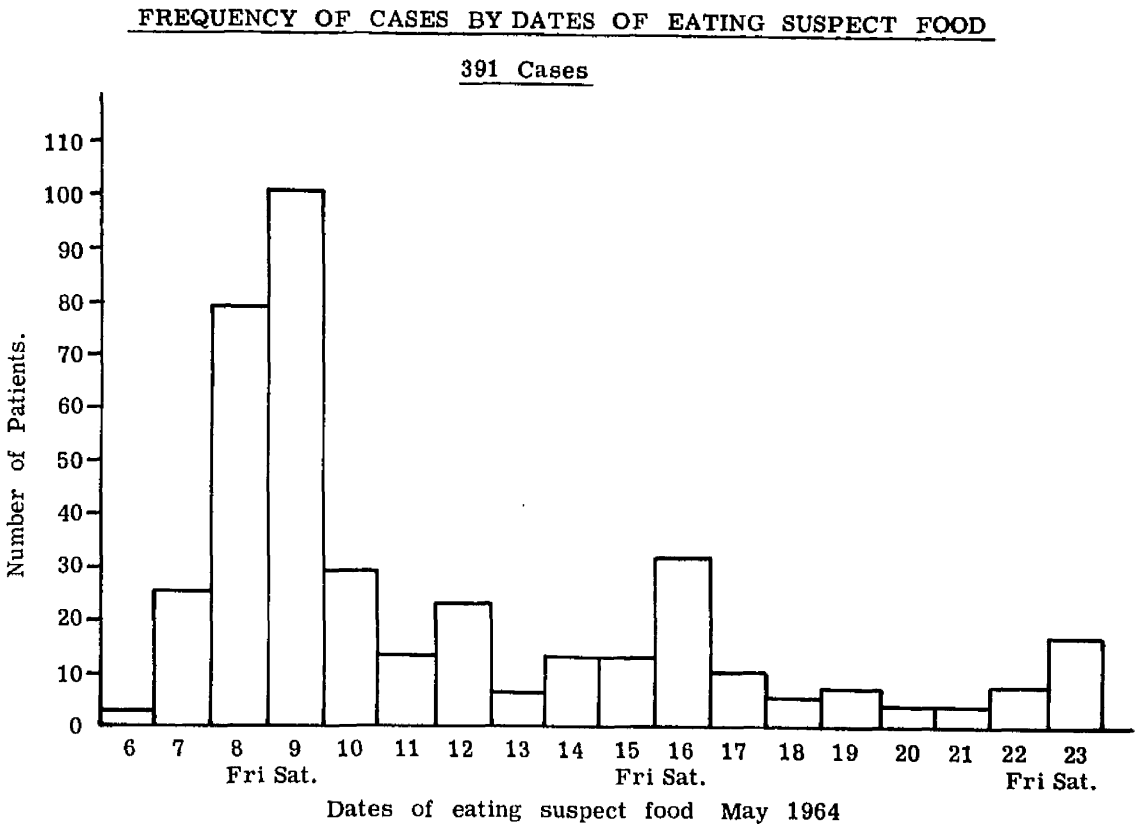


Fig. 4 - Frequency of cases by dates of eating suspect food - 391 cases.

A "typhoid patient" is defined as one who contracted typhoid fever in Aberdeen and had at least part of his investigations carried out there. A further 8 persons contracted typhoid fever while visiting Aberdeen but were treated elsewhere: 3 in Glasgow, 2 in Newcastle, 2 in Dundee and 1 in Toronto. All were shown to be infected by the same 'phage-type of S. typhi.

C. THE DEVELOPMENT OF THE OUTBREAK

(1) Development in Time

The outbreak took the shape of a single wave, and there were no proved secondary cases.

The first 30 patients gave a history of eating, amongst other things, cold meat from a supermarket in the West End of Aberdeen City. The types of meat incriminated were various, but 17 of the 30 had eaten corned-beef, the first date of buying being the 6th of May. In all, a history of eating food from the shop was given by 391 patients covering a period of 18 days. The number of patients known to have eaten infected food on each individual day is shown in Figure 4. Of the 391 patients shown, 373 ate cold meat and 18 ate fruit. It is interesting to note the increase in sales

of cold meat at each week-end. These sales were higher than usual since, unfortunately, there was a corned-beef sales drive during the first week of infection! It is probable that, although the organism was never isolated from the shop, infection on saleable goods would have continued to spread the disease had not the public stopped buying food there after 23rd May. Some of the histories of exposure obtained from patients support the view that the infection was disseminated throughout the shop. For example, a child of 4 years was taken to the shop by her mother, who bought no food. The child, however, was reprimanded for licking the hand-rail at a food counter. The child later developed typhoid fever, although no one else in the family was affected and she had no other contact with a case.

The history of exposure to infection of the 507 patients is shown in Table 9.

Those patients with a history of "family contact" all became ill at approximately the same time as the rest of their household. It is, therefore, assumed that the organism was passed by mechanical transfer from the original source, and not via the excreta of an infected case. Thus, these were not cases of secondary spread.

TABLE 9

HISTORY OF EXPOSURE TO INFECTION GIVEN BY 507 PATIENTS

ATE FOOD FROM INFECTED SHOP -	MEAT	373
	- FRUIT	18
FAMILY CONTACT ONLY		32
NO KNOWN EXPOSURE TO INFECTION		84
TOTAL:		507

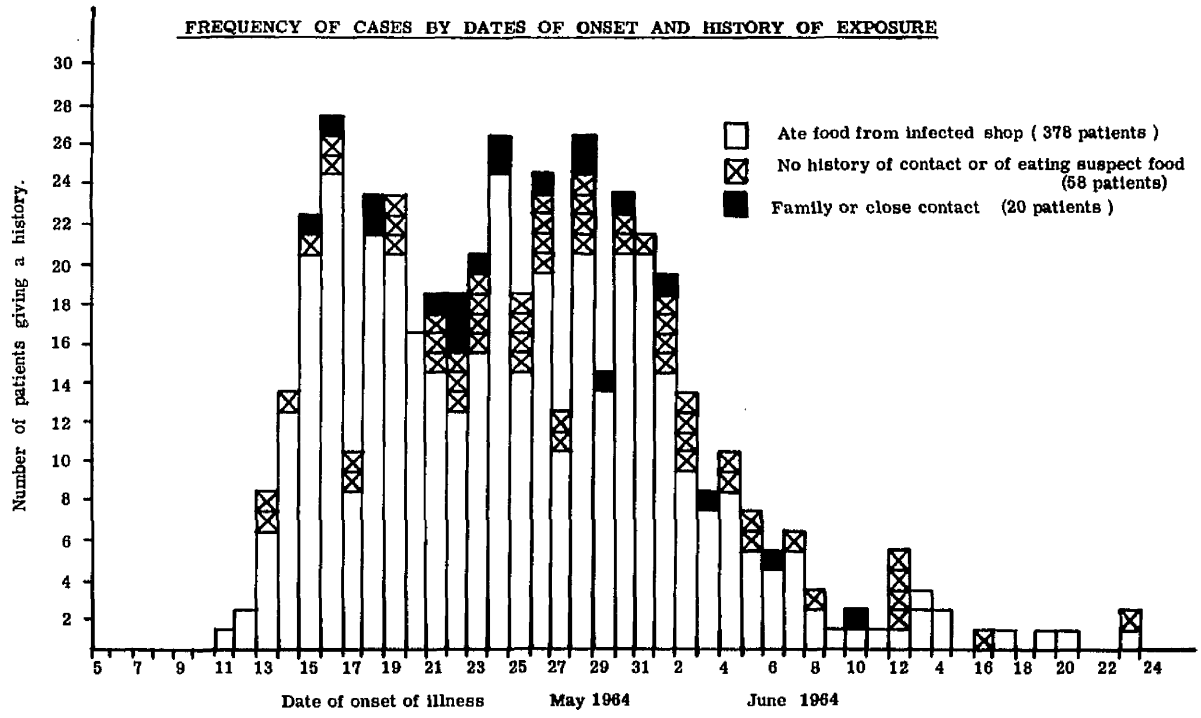


Fig. 5 - Frequency of Cases by Dates of Onset and History of Exposure.

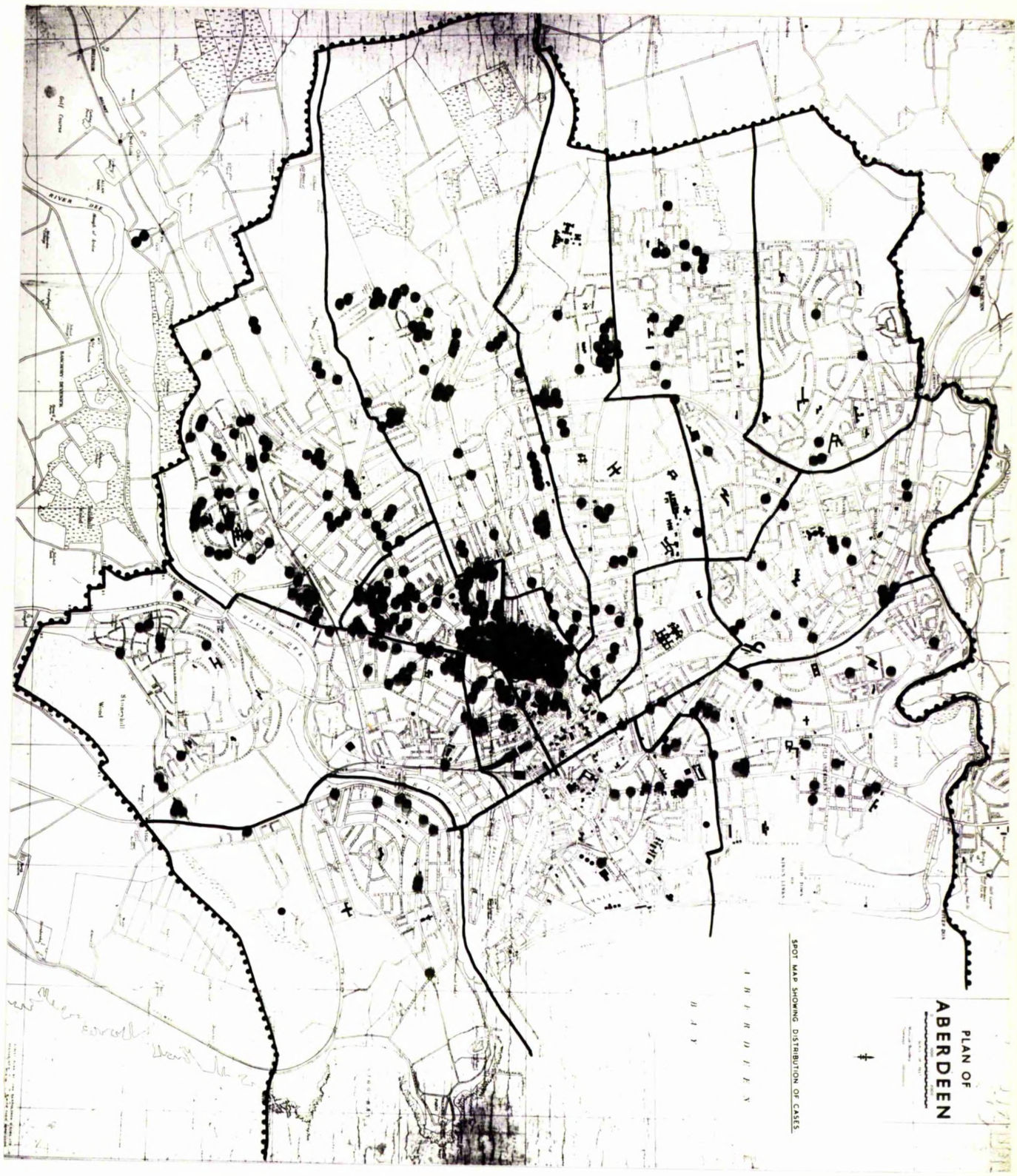


Fig. 6 - Map of Aberdeen showing the Distribution of Typhoid Patients

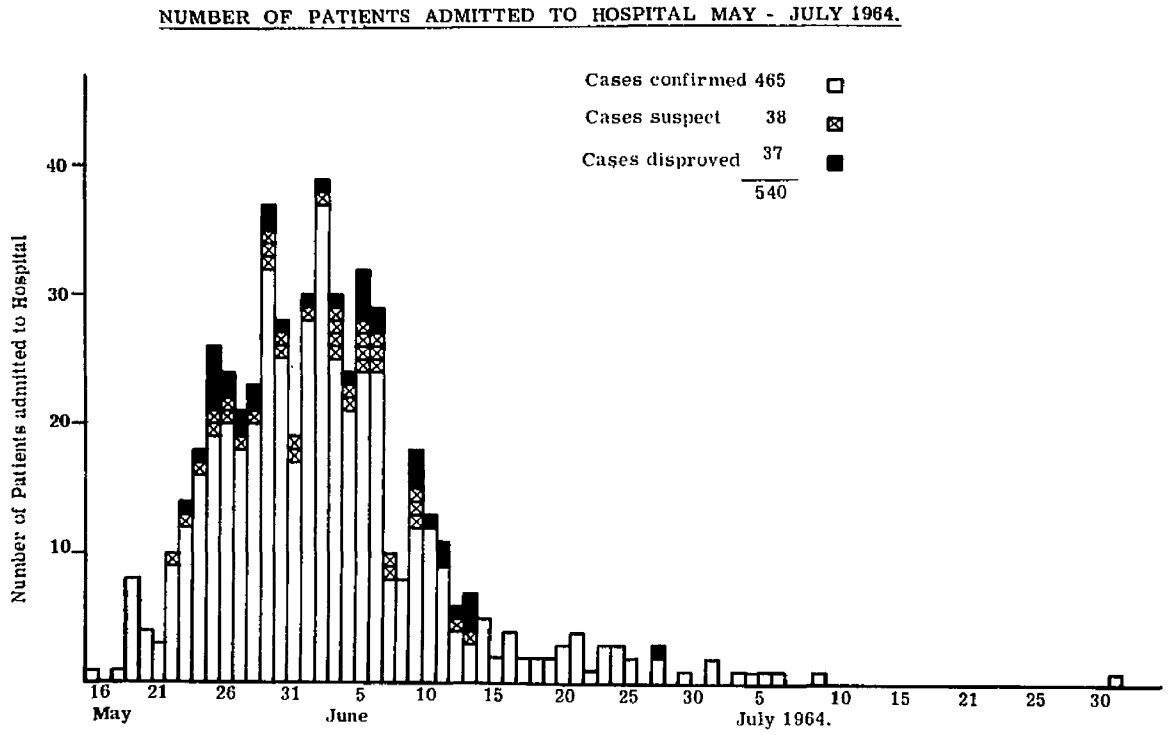


Figure 7. The rate of Admission of Typhoid Patients to hospital during the outbreak, distinguishing subsequent confirmation of diagnosis.

In Figure 5, which relates history of source to date of onset of illness, this date is taken as the first on which any symptom attributable to typhoid was felt, but excludes the short-:lived diarrhoea which occurred in 6 patients very soon after eating infected food.

The date of becoming ill was determined accurately in 456 patients.

(ii) The Development in Space

The first cases admitted to hospital came from widely divergent areas of Aberdeen, with different water and milk supplies. At one point in the first few days it appeared that the patients were sited along one of the five main water supply routes, but with the increase in cases it became obvious that the majority came from the area of Aberdeen surrounding the incriminated supermarket. This shop was situated at the more prosperous end of the shopping centre which was served by all the main bus routes, and cases occurred in all the suburbs of Aberdeen. Figure 6 shows the distribution of cases in the city. Patients came from 309 house-:holds in the city, that is, less than 0.6% of the 58,000 households in Aberdeen. Aberdeen is still the main shopping centre for the North-East of Scotland, and a further 42 cases came from 33 house-

:holds in the surrounding districts, some as far as 70 miles from Aberdeen.

D. THE ADMISSION OF PATIENTS TO HOSPITAL

Figure 7 shows the rate of admission of typhoid patients to hospital, distinguishing cases subsequently confirmed. This graph excludes the last patient, who was admitted on 31st July.

There were four other cases not admitted to hospital, all of whom were asymptomatic and were tested as contacts. The sera of three of them showed a significant rise in S. typhi H agglutination and the fourth case had S. typhi isolated from faeces. This last patient refused further examination for some time but was later persuaded to co-operate, when six weekly stool and urine specimens were negative, but she had S. typhi H serum agglutinins at 1:25 dilution.

(i) Criteria for admission to hospital

The first patient was admitted to the City Hospital, Aberdeen on 16th May, 1964 with pyrexia of unknown origin. At the same time there were two students in Aberdeen Royal Infirmary with

the same diagnosis who were subsequently confirmed as having typhoid fever. In the next few days 2 patients were admitted with suspected appendicitis, 3 with "gastro-enteritis" and 3 with pyrexia of unknown origin, all of whom later were found to have typhoid fever.

After the first positive diagnosis on 20th May rumour of the outbreak spread, and a further 45 cases were admitted to hospital before official notification of the disease was given on 25th May by the Public Health Authorities. Thereafter the admission rate rose rapidly.

Prospective hospital patients were examined and/or tested at home, either because they were ill or as contacts of a suspected case. It soon became obvious that some typhoid patients were presenting with only a mild illness similar to "influenza", and also that there were many ex-servicemen who had had T.A.B. vaccine in the past. Thus, to admit patients on the grounds of either clinical picture or positive serum agglutination tests without supportive evidence might have led to persons being admitted in error. In order to avoid this, the general practitioners were given certain lines of guidance by the hospital and laboratory staff for cases where the diagnosis was not certain. These were:-

(a) If the patient was extremely ill, immediate admission to hospital was indicated.

(b) If the patient was not so ill that a few hours' delay would be harmful, it would be helpful to have serum antibody assays performed before admission, in an attempt to separate proved and suspect typhoid cases in hospital.

(c) If the patient was only mildly ill or was well but had a positive Widal reaction when tested as a contact, it would be valuable to know whether or not he or she had previously been immunised. If there had been no immunisation, admission was indicated. In immunised cases a repeat Widal test was to be done in a few days' time and the patient then admitted if a significant rise in serum antibody level had occurred.

All admissions to hospital were assayed through a central office. All positive bacteriological or serological results were telephoned from that office to the general practitioner concerned and to the appropriate Medical Officer of Health. The former dealt with the patient, either by arranging his admission or by taking a further blood specimen in a few days' time, while the latter dealt with the contacts of each new case.

On the basis of the above suggestions, the following criteria for admission as a case of typhoid fever were suggested:-

1. Any combination of (a) <u>suspicious symptoms</u>

(b) a history of exposure to infection

i.e. consumption of food from the suspected shop or family contact with a known case.

(c) a positive Widal's reaction

i.e. any titre of serum agglutination in an uninoculated person and a rise in titre of more than one tube in a previously inoculated person.

It should be stated here that, in view of the increasing pressure on laboratory services, only an abbreviated test of S. typhi H agglutination to a maximum of 1:400 dilution was possible.

2. Isolation of the organism from any specimen of blood, faeces or urine.

Isolation of S. typhi from any one specimen was considered to be diagnostic of typhoid fever in that patient. In the initial onslaught of admissions, however, a clear clinical picture of typhoid combined with a diagnostic level of serum agglutinins in the uninoculated was taken as sufficient proof of the disease and, while a few of these patients gave a positive isolation of S. typhi either on relapse or during convalescence, some remained only clinically confirmed. A case was considered to be confirmed clinically when there were typical signs of typhoid fever, that is, rose spots and

splenomegaly. A case was classified as "not confirmed" when the clinical picture, although suggestive of typhoid fever, was not diagnostic and when, in the uninoculated, there was no supportive serological evidence. In the inoculated patient, the presence or even an increase of serum agglutinins was not considered in itself to be diagnostic.

Table 10 shows the reasons for admission of the 503 confirmed or probable cases of typhoid fever, and Table 11 shows those subsequently confirmed in each group. There were seven main categories on which admission was based:-

1. "symptoms alone"
2. "symptoms + Widal"
3. "symptoms + history"

   380 patients (75%) were admitted for these three reasons, only 74 (14%) severe cases being admitted on the grounds of symptoms alone. Of these 380 patients, 356 (94%) were subsequently confirmed.

   This may be interpreted in one of two ways: firstly, that symptoms sufficient to warrant admission to hospital were seldom wrongly diagnosed at home, or secondly, that in patients with obvious symptoms, bacteriological or serological proof of typhoid infection was easier to obtain than in patients who were less ill.

4. "history + Widal"
5. "Widal alone"
6. "history alone"

TABLE 10

REASONS FOR ADMISSION TO HOSPITAL,
SHOWING SUBSEQUENT CONFIRMATION OF DIAGNOSIS

REASON FOR ADMISSION	NUMBER OF PATIENTS	NUMBER CONFIRMED
POSITIVE ISOLATION:		92
- BLOOD	1	
- CLOT	28	
- STOOL	62	
- URINE	1	
SYMPTOMS ALONE	74	66
SYMPTOMS AND HISTORY	143	138
SYMPTOMS AND WIDAL	163	152
HISTORY AND WIDAL	18	9
WIDAL ALONE	4	2
HISTORY ALONE	9	6
	503	465

TABLE II

SUBSEQUENT CONFIRMATION OF DIAGNOSIS IN PATIENTS ADMITTED FOR REASONS OTHER THAN POSITIVE ISOLATIONS

REASON FOR ADMISSION	CONFIRMATION OF DIAGNOSIS				DIAGNOSIS NOT CONFIRMED	TOTALS
	CLINICAL	BACTERIOLOGICAL				
		ON ADMISSION	ON RELAPSE	AFTER DISCHARGE		
SYMPTOMS ALONE	17	47	2	0	8	74
SYMPTOMS AND HISTORY	7	125	3	3	5	143
SYMPTOMS AND WIDAL	37	108	4	3	11	163
HISTORY AND WIDAL	0	8	1	0	9	18
WIDAL ALONE	2	0	0	0	2	4
HISTORY ALONE	0	6	0	0	3	9
TOTALS:	63	294	10	6	38	411

22 patients (4%) were admitted because of a positive Widal reaction with or without a history or exposure to infection. In exactly half of them the diagnosis could not be confirmed by subsequent laboratory tests. All of these had had T.A.B. injections in the past, although at the time of admission this was sometimes not known. Only 9 patients (2%) were admitted solely because of a history of exposure to infection. All of these were admitted, for social reasons, with other members of the same family; in three the suspicion of typhoid could not be confirmed.

7. "positive isolation"

In 92 cases (18%) S. typhi was isolated before admission to hospital. One of the first patients had a blood culture performed at the request of his general practitioner, but in all other cases clot culture was performed routinely on specimens of blood sent for serology. In 28 patients (6%) a positive clot culture so obtained was the reason for admission to hospital.

A further 62 patients (12%) were admitted because of positive faeces culture. Only one patient was admitted because of S. typhi found in urine.

Ashcroft (1964) stated that "the protection given by vaccines from bacteriological diagnosis cannot be assumed to be identical with protection from infection", and he also believed that immunisation modified the course of the disease, making clinical diagnosis difficult.

The confusion caused by previous immunisation when the diagnosis was uncertain is illustrated by the number of unconfirmed cases who had had T.A.B. vaccine in the past, namely 28 of the 38

cases who remained only suspect (see Table 12). The distribution of inoculated and uninoculated patients in the three diagnostic groups was compared, and showed significantly more immunised individuals amongst those bacteriologically than amongst those clinically confirmed ($x^2 = 25.72$ $P < 0.0005$) and also more amongst those clinically confirmed than amongst those in whom the diagnosis remained unproved ($x^2 = 11.60$ $P < 0.001$).

(ii) Patients in whom the diagnosis of typhoid fever was not confirmed.

There were 38 patients in whom it was not possible to obtain satisfactory proof of typhoid infection. It has been stated already that in those who had been previously inoculated, S. typhi H agglutination was of doubtful value. The reason for this is that even a rise in titre might have been due to an anamnestic or non-specific reaction caused by some other febrile illness. In these, as in most other cases, S. typhi "O" agglutinins were not assayed on admission because of pressure of work in the laboratory; some were done later but were negative, and all were negative on discharge. However, of these patients one had S. typhi 'O' agglutinins at 1:50 dilution at three-month follow-up examination, and seven had S. typhi 'O' agglutinins at 1:25 to 1:100 dilution at six-month follow-up examination. The finding of 'O' agglutinins supports

TABLE 12

ABERDEEN TYPHOID OUTBREAK, 1964

PROPORTIONS OF INOCULATED PATIENTS IN EACH DIAGNOSTIC GROUP

	DIAGNOSTIC CONFIRMATION		NOT CONFIRMED	TOTALS
	BACTERIOLOGICAL	CLINICAL		
INOCULATED	61 (.2)	28 (.4)	30 (.8)	119 (.2)
UNINOCULATED	342 (.8)	38 (.6)	8 (.2)	388 (.8)
ALL TYPHOID PATIENTS:	403 (1.0)	66 (1.0)	38 (1.0)	507 (1.0)

the suspicion that these individuals did, in fact, have typhoid fever, since it is rare to find 'O' antibodies except where there has been recent infection (Felix, 1930).

Clinical examination in all 38 cases was negative as regards typhoid fever. One patient had transient hepatomegaly which, however, might have had another cause, and eleven of these patients were asymptomatic. The remainder were not severely ill; their symptoms could have been attributed to upper respiratory infection, urinary infection, gastro-enteritis and similar ailments, although no other organisms were isolated. A history of exposure to infection was given by 26 of the 38.

Suspicion of infection must remain in these patients since there were other proved cases whose symptoms were identical and, as will be shown later, other proved cases who showed no antibody response. It is likely that, had there been an opportunity to observe and test all patients more closely, the diagnosis of typhoid fever might have been confirmed in a greater number.

(iii) Other Patients admitted to Hospital during the Outbreak

There were 37 patients admitted to hospital during the outbreak in whom the diagnosis of typhoid fever was entertained

but finally discarded, 7% of the 540 patients admitted. All but 8 of these were admitted only by reason of symptoms. Of these 8, 3 were neonates whose mothers were suspected or confirmed cases prenatally, 3 others had positive agglutination reactions which were later felt to have been erroneous, and 2 were contacts admitted for social reasons. There were 10 cases of gastro-enteritis (called "non-specific" because of the absence of any positive laboratory findings despite repeated testing). Of the rest, 4 had severe upper respiratory infection, 2 had proved B. coli urinary infection, 2 had measles and 1 rubella. The remainder had an interesting variety of conditions, for example empyema of gall-bladder, staphylococcal septicaemia, myocardial infarction, subarachnoid haemorrhage and salpingitis. One man who worked for a refrigeration company had phosgene poisoning, and a child whose "best friend" had typhoid fever was proved bacterio-:logically to have Sonne dysentery. One man demanded admission because his wife and son were proved cases of typhoid. Often the admission of these patients was more to allay anxiety on the part of either patient or general practitioner, but if one considers the extent of the panic engendered in Aberdeen, it is on the whole remarkable that there were not many more such cases.

CONCLUSIONS

From the relatively small number of patients who did not have typhoid fever, the criteria for admission to hospital which were used in this outbreak appear to be justified, but they require reasonable home circumstances and good co-operation between practitioners and hospital. The abbreviated agglutination reaction used here was done in six hours, and few patients were too ill to await the result before admission. The General Post Office provided a continuous delivery service of specimens to the laboratory, and special clinics were organised by the general practitioners for the testing of contacts. In a less well-doctored area, more work would have had to be delegated to the Public Health Medical Officers.

E. THE OUTCOME

(i) Criteria for "Clearance"

The majority of the patients were considerably improved after a few days of treatment and some difficulty was experienced after the first week in detaining patients who had an uncomplicated convalescence in bed. This "sense of well-being and eagerness to be up and doing" was also observed by Torrens (1923) in many typhoid patients during the First World War, and is not apparently a

particular feature of chloramphenicol-treated typhoid fever. It became obvious that even greater difficulty would arise in persuading patients to remain in hospital for a protracted "clearance" programme. It was, therefore, arbitrarily decided that all patients should obtain only three consecutive negative specimens of both faeces and urine at four-day intervals before being discharged from hospital, and that the remaining negative specimens required would be obtained after discharge. The first specimen was taken four clear days after the end of treatment for the acute illness. The number of consecutive paired negative specimens required after discharge depended on the extent of each patient's contact with food and the general public.

There were three categories of such contact:-

1. Professional foodhandlers who had to submit 9 consecutive negative results at weekly intervals before being allowed to return to work.

2. Housewives, school teachers and other individuals with many contacts required 6 negative specimens at weekly intervals.

3. All other patients required three such paired specimens before being considered to be cleared of infection.

It was also decided to continue to test all patients at intervals over the following two years in order to increase the

chances of identifying any intermittent carriers who might result from the outbreak. Accordingly, a "follow-up" programme was agreed, consisting of three paired specimens of faeces and urine at weekly intervals repeated at 3, 6, 12 and 24 months after discharge from hospital. Specimens of faeces were taken after the administration of a saline purge. Samples of blood were taken from each patient at the time of discharge. This was for estimation of serum agglutinins, including Vi antibody, and also for examination of the blood picture, in view of the possibility of aplastic anaemia following chloramphenicol therapy (Hodgkinson, 1954).

(ii) The Incidence of the Carrier State

There were 159 convalescent excreters (33.9%) of whom 5 at least became chronic faecal carriers. These carriers will be discussed in detail in Section VII. There were two temporary urinary excreters, but none known who became chronic carriers. The chronic carrier rate of approximately 1% is remarkably low. It will be considered later whether this was a feature of the organism, since one of the same 'phage-type also produced a very low carrier rate at Oswestry in 1948, or whether it was a result of the treatment used in Aberdeen.

F. SOME CHARACTERISTICS OF THE PATIENTS

All subsequent data in this thesis are based only on the 469 patients in whom the diagnosis was proved.

(i) Age and Sex Distribution

The age and sex distributions of the 469 proved typhoid patients are shown in Table 13. There was a preponderance of young women in the 15 - 29 age group, the reason for this being the number of young, single women who were on a reducing diet of cold meat and salad. Figure 8 shows the proportionate age and sex distributions of the cases compared with those of the population of Aberdeen (Census 1961).

(ii) Social background

The Social Class distribution of the employed, adult typhoid patients showed that 29% were in the Registrar General's Social Classes I and II, as opposed to only 15% of the employed, adult population of Aberdeen city at the 1951 Census. This corresponded with a relatively high incidence in the more prosperous wards of the city.

TABLE 13

AGE AND SEX DISTRIBUTION OF THE PROVED TYPHOID PATIENTS

AGE GROUPS IN YEARS	MALES	FEMALES	BOTH SEXES
0 - 14	53	55	108
15 - 29	37	89	126
30 - 44	37	38	75
45 - 59	26	60	86
60'S AND OVER	29	45	74
ALL AGES	182	287	469

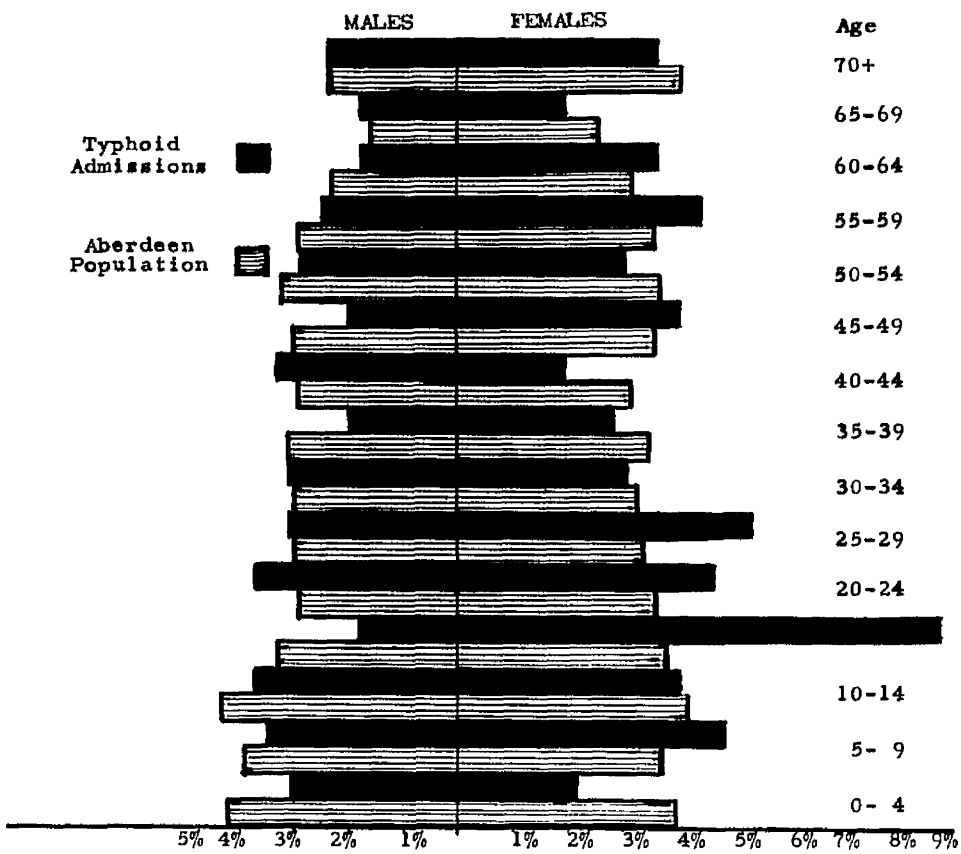


Fig. 8 - The proportionate age and sex distribution of the Typhoid Patients, compared with that of the Population of Aberdeen (Census 1961).

TABLE 14

PERCENTAGE DISTRIBUTION OF OCCUPIED AND RETIRED ADULTS IN ABERDEEN CITY AND IN THE TYPHOID POPULATION BY SEX, DISTINGUISHING SOCIAL CLASS

SOCIAL CLASS	MALES		FEMALES	
	CITY	TYPHOID POPULATION	CITY	TYPHOID POPULATION
I	3.5	7.5	0.9	2.6
II	12.1	20.0	17.8	28.7
III	53.1	52.5	52.0	52.2
IV	14.3	12.5	16.7	13.9
V	17.0	7.5	12.6	2.6

The living conditions and food habits of the typhoid patients were studied in order to obtain a picture of the social background of the outbreak. The relatively large number of patients in Social Classes I and II was reflected here: 69% of the patients had a bathroom in their house and 82% had continuous hot water. A washbasin beside the lavatory was available to 74% although 29% shared a lavatory with other families.

90% of patients maintained that food was not kept in their houses for longer than three days; only one patient confessed to keeping food for longer than a week. Ease of transport in Aberdeen made it possible for 78% of patients to have their mid-day meal at home, and the same number stated that they seldom ate outside their own homes.

The number of young people involved in the outbreak produced a large number of contacts; 43% of patients had more than 30 personal contacts each day. More than 20% were schoolchildren, and there were quite a few young girls who went to dance halls. In the event, about 10,000 contacts were tested, many of whom went voluntarily to their general practitioners, but none was found to have contracted typhoid fever through contact with a known case.

Only 10% of patients had been abroad in the previous 2 years, and none of these had suffered any illness while abroad. Thus, the typical typhoid patient emerged as a quiet-living citizen with excellent facilities for personal hygiene.

(iii) Incubation Periods

The incubation period of typhoid fever is usually 10 - 14 days but incubation periods as short as 5 days and as long as 35 days have been recorded (Wilson and Miles, 1965). It is sometimes difficult to ascertain accurately the date of onset of illness: in this outbreak there were 6 patients who had short-lived diarrhoea within 12 hours of consuming infected food, but who had no generalised illness at this stage. This initial symptom was presumably caused by local irritation in the gut, and therefore was discounted in the calculation of the incubation period.

Two patients had an incubation period of only 2 days, and 3 had an incubation period of 3 days. There were 77 patients with an incubation period of 7 days or less. At the other end of the scale there were 61 patients with an incubation period of 20 days or more, the longest certain one being 39 days. The last patient of the outbreak had initial diarrhoea for one day and then an interval of 56 days before he became ill, but the fact that he

had jaundice and epigastric colic at this stage suggests that this was a cholangitis following a very mild initial infection. Details of 378 incubation periods are shown in Appendix II (a) and a summary of the mean incubation periods related to different factors is shown in Table 15.

The mean incubation periods of adults and children were not significantly different. The incubation periods of patients who relapsed and of temporary carriers were not significantly different from those of other patients, nor were those of patients who had been immunised.

It was thought that the incubation period might vary with the dose of the organism ingested, a large dose producing clinical illness more quickly than a small one. The dose of the organism could not be assessed, but since this, in turn, might be related to the severity of the initial infection, the length of the incubation period was correlated with the severity of the initial infection in all patients in whom it was certain. The only obvious conclusion which could be drawn was that there were proportionately more patients with a mild illness on admission whose incubation period was longer than 21 days. However, a long incubation period gives rise to the suspicion that there

TABLE 15

SUMMARY OF MEAN INCUBATION PERIODS IN 378 PATIENTS WITH A HISTORY OF EATING INFECTED FOOD

	NUMBER	MEAN INCUBATION PERIOD (DAYS)
ALL PATIENTS	378	13.1
ADULTS	300	12.8
CHILDREN	78	14.4
RELAPSE	86	12.2
OTHER	292	13.4
INOCULATED	57	12.8
UNINOCULATED	321	13.1
EXCRETER	144	12.9
OTHER	234	13.2

was an asymptomatic initial infection, and that the patient was admitted in relapse, and little importance can be attached to this finding.

CONCLUSIONS

Incubation periods were examined to discover whether they differed according to age, the occurrence of relapse, the temporary carrier state, and the immunisation state of the patients. No significant differences could be demonstrated.

A possible connection was shown between a mild infection and a long incubation period, but this must be regarded with caution.

G. SOME CLINICAL FEATURES OF THE OUTBREAK

(1) Presenting symptoms

Most patients were admitted to hospital towards the end of the first week of illness, the mean day of illness on admission being 6.3 days with a range of 2 to 27 days. The clinical history given by patients varied with successive weeks of the outbreak. Patients who were admitted in the first week of the outbreak had in the main a history of headache and malaise for 12 - 24 hours before the onset of severe gastro-

enteritic symptoms lasting for 2 - 4 days. Classical symptoms of typhoid fever followed a day later, that is, high fever, dry cough, severe headache and abdominal pain and distension.

The severe diarrhoea which occurred in 44 patients in the first week of illness is more often seen in the first stages of paratyphoid fever and is unusual in typhoid. A few stool cultures taken during the period of diarrhoea gave a heavy growth of S. typhi, and no concomitant pathogens were found to account for the diarrhoea.

Patients admitted in the second week of the outbreak showed the more typical slow onset of illness. A mild, influenza-like illness for 24 - 48 hours was followed, sometimes immediately, but more frequently after a period of remission of 2 - 3 days, by classical typhoidal symptoms. A similar afebrile period of remission was observed by Marmion (1952) in some cases in Egypt. Headache and high fever were almost invariably present; only two patients in the outbreak had a purely gastro-enteritic illness. Sore throat and vomiting were unusual in adults but were seen in children. During the second week, the first patient to have a positive faeces specimen but only a mild illness was admitted. This particular patient, who had been immunised in 1940-45, did not at any time have pyrexia above

99°F. but relapsed after discharge from hospital and was re-admitted with a positive blood culture although afebrile.

From the third week of the outbreak onwards, there were progressively more patients admitted because of positive isolations from blood clot, faeces or urine; of the last 30 patients admitted, 17 had a positive faeces culture before admission. Some of these patients were symptom-free and gave rise at first to much discussion as to the veracity of the laboratory findings. Other controversial cases were admitted at this time, for example six persons who had just been immunised. Four of them were later proved to have typhoid fever.

The incidence of signs and symptoms on Aberdeen patients is shown in Table 16.

(ii) The Occurrence of Initial Gastro-enteritis

Wilson and Miles (1965) state that "the typical symptoms of the disease may be preceded by acute gastro-enteritis coming on shortly after consumption of infected water or food. These early symptoms may pass imperceptibly during the following week or so into those characteristic of enteric fever, or there may be a remission before the onset of enteric symptoms, or there may be a complete and lasting recovery." The cause of this is

TABLE 16

FREQUENCY OF CLINICAL FEATURES IN THE 469 PATIENTS

SIGN OR SYMPTOM	FREQUENCY	PERCENTAGE OF 469
HEADACHE	375	80.0
FEVER	368	78.5
MALAISE	331	70.6
RESPIRATORY	182	38.8
DIARRHOEA	195	41.6
CONSTIPATION	185	39.4
ABDOMINAL PAIN	160	34.1
MUSCLE PAIN	120	25.6
VOMITING	117	24.9
ROSE SPOTS	234	49.9
SPLENOMEGALY	196	41.8
HEPATOMEGALY	76	16.2
EPISTAXIS	99	21.1
RIGOR	81	17.3
MENINGISMUS	62	13.2
DEAFNESS	60	12.8
DEHYDRATION	45	9.6
DELIRIUM	37	7.9
MENSTRUAL DISORDERS	17	3.6

uncertain, but a possible explanation is given in Section V, (page 190).

All three types of early gastro-enteritis occurred in Aberdeen. Two patients, one of whom was the first typhoid patient admitted to hospital, had diarrhoea, starting a few hours after eating infected food. In both cases the diarrhoea continued for 4 - 5 days and then both became ill with generalised typhoidal symptoms. Four other patients were known to have had diarrhoea without systemic illness within 12 hours of exposure to infection, followed by a period of remission of 3 - 10 days before the onset of typical typhoid fever. One woman ate jellied veal, had acute diarrhoea and vomiting for 12 hours, and did not develop typhoid, whereas her son ate the same meal and developed typhoid fever 8 days later. None of these patients had stool specimens taken during the initial diarrhoea. There is no obvious factor common to them with regard to date of eating or quantity and type of cold meat consumed.

(iii) Some Observations on the Physical Signs of Typhoid Fever

The physical signs observed in this outbreak were in the main those of classical early typhoid fever. The incidence

of rose-spots and splenomegaly was relatively high, probably because of the early admission of patients. Meningismus was common in the early cases - the first patient of the outbreak had a lumbar puncture performed because of marked meningeal irritation. Two features deserve special mention:-

(1) Bradycardia

It has long been said in textbooks that bradycardia relative to pyrexia is usually found at least in the first week of typhoid fever. However, Gay (1918) described "a slow pulse of 100-110" and by this criterion "bradycardia" may certainly occur. The findings in this outbreak were that the pulse rate, even in the first week of illness, was usually proportional to the height of pyrexia. The mean pulse rate on admission was 106 per minute, with a range of from 72 per minute in afebrile patients to above 140 per minute in ill patients. In children the mean pulse rate was 122 per minute with a range of 95 per minute to above 140 per minute. It is interesting to note that earlier observers, for example Jenner and Budd, did not find bradycardia, although the faster pulse noted then may have been caused by the dehydration and toxicity of the later stages of typhoid.

(2) Leucopenia

Leucopenia was not found in as many patients as expected although patients might have been admitted before it had time to develop, and low blood counts during the administration of chloramphenicol might have been due to its possible suppressive effect (Scott et al 1965). A white cell count was performed in 310 cases on admission; the results of these are shown in Table 17. There was no constant relationship between severity of illness and the level of the white cell count.

TABLE 17

LEVELS OF 310 WHITE CELL COUNTS ON ADMISSION

DISTINGUISHING "SEVERITY OF ILLNESS"

LEVEL OF WHITE CELL COUNT	SEVERITY OF ILLNESS			
	MILD	MODERATE	SEVERE	TOTALS.
LESS THAN 4,000	15	15	34	64
4,000 TO 5,000	13	21	48	82
5,001 TO 8,000	38	28	62	128
OVER 8,000	15	8	13	36
TOTALS:	81	72	157	310

Bauer (1951) commented on the difficulty of diagnosing typhoid fever in children, since so many of them showed atypical clinical features and no leucopenia. One case in Aberdeen illustrates this very well:-

> A girl of nine, with no history of exposure to typhoid infection, was admitted to hospital because of a six-day history of fever with rigors, headache, listlessness and sore throat. A throat swab gave a growth of Staph. albus only, and her white cell count was 10,850 with 73% neutrophil polymorphs. Blood, faeces and urine cultures on four successive days revealed no organisms. A course of oxytetracycline, which had been started before admission, was continued for 5 days, and her temperature settled on the third day of this treatment. However, it recurred 6 days later, reaching 102°F. Serum agglutination at this stage showed only S. typhi 'H' agglutinins to a dilution of 1:25, but the Paul Bunnell test was positive to a dilution of 1:16; the white cell count was 6,900 with 60% neutrophil polymorphs. Blood culture was negative, but five days later S. typhi was isolated from her faeces. She responded well to chloramphenicol therapy and convalescence was uneventful.

(iv) An Assessment of the Severity of the Illness

The severity of any illness is difficult to express accurately, and typhoid fever is more difficult than some because its severity appears to vary with different strains in different outbreaks (Marmion, 1952). If a classification of "severity" is based solely on clinical impression, it will inevitably vary with different observers. With chloramphenicol therapy the illness is suppressed after a few days of treatment, and the

signs of severe toxaemia with meteorism and "the typhoid state" are seldom seen. Any classification should, if possible, be based on measureble factors which may be compared in different outbreaks and which do not show subjective variation.

Ashcroft (1964), during a field trial of T.A.B. vaccines in British Guiana, grouped his cases of typhoid fever according to the severity of the illness, thus:-

(a) Severe - all deaths, relapses and cases with complications.

(b) Moderate - all cases with a temperature of 100°F. and over for 4 days or more.

(c) Mild - all other cases including those not admitted to hospital.

While this classification allowed comparison with other outbreaks, it was felt that it did not adequately describe patients who were extremely ill on admission to hospital but who had no complications. Moreover, in many cases the temperature was reduced to normal within 4 days by chloramphenicol therapy. Accordingly, Ashcroft's definition was modified, and the following is the classification of the severity of the complete illness which was used in Aberdeen:

(a) Severe - all patients with a temperature of above 102°F. for 2 days or more, and all cases of death, relapse or complication.

(b) Moderate - all patients with a temperature of 100°F. to 102°F. for 2 days or more.

(c) Mild - all other cases with symptoms

(d) Asymptomatic - all patients with no symptoms

However, cases of death, relapse, or complication could not be included in the classification of "severity" when its effect on the course of the disease (for example, on the incidence of relapse) was considered. It was, therefore, decided for this purpose to classify the severity of the initial infection according only to the extent of the initial pyrexia. In theory this meant that cases of death, relapse or complication might have two different classifications of severity - one based on the initial illness and one on the overall course of the disease. In practice, only a few cases of death, relapse or complication were not severely ill on admission. In order to distinguish the use of the two categories, however, the terms "severity of the initial infection" and "severity of illness" have been used.

The number of patients in each group, distinguishing age and sex, is shown in Appendix II.3(a). The severity of the illness/

is indicated thus:-

Asymptomatic	=	0
Mild	=	1
Moderate	=	2
Severe	=	3

Table 18 shows the percentage age and sex distributions of patients with different degrees of severity of illness. Because of the disparity in numbers between each group, symptomless and mild cases are shown together, as are moderate and severe cases. For the same reason, symptomless and mild cases are grouped together in most of the subsequent calculations of differences in degrees of severity of illness related to various factors. All calculations which showed a significant difference are to be found in Appendix III.

It may be seen from Table 18 that there was a significant difference between the sexes in the severity of the illness, 30% of males having asymptomatic or mild typhoid fever, as opposed to 16% of females ($\chi^2 = 11.94$, $P < 0.01$). When this sex difference was examined in age groups it was found to be just significant in only the two age groups 45 - 59 and 60 and over, although the same trend was seen in all age groups. There was no difference in "severity" between males of different

TABLE 18

"SEVERITY OF ILLNESS" OF TYPHOID PATIENTS

DISTINGUISHING AGE AND SEX

PERCENTAGE DISTRIBUTION.

AGE GROUPS	MALES		FEMALES	
	GRADES OF SEVERITY		GRADES OF SEVERITY	
	0 + 1	2 + 3	0 + 1	2 + 3
0 - 14	21%	79%	11%	89%
15 - 29	27%	73%	15%	85%
30 - 44	30%	70%	26%	74%
45 - 59	46%	54%	20%	80%
60 &-OVER	38%	62%	13%	87%
ALL AGES:	30%	70%	16%	84%

age groups or of females of different age groups.

It will be shown in Section IV that previous immunisation appeared to mitigate the course of the disease.

The comparison of the severity of the illness in age and sex groups was, therefore, repeated for uninoculated patients only. It was found that there was no significant difference in severity between uninoculated males and females either as a whole or in separate age groups. It would appear, therefore, that the significant difference in the number of males and females aged 45 and over who had only a mild illness was due to the fact that many more of the males were immunised.

It was thought that patients who were more severely ill initially might take longer to respond to treatment. The duration of pyrexia on treatment and the severity of the initial infection were compared. Since most of the patients who had a mild illness had, by definition, either no pyrexia or pyrexia for less than two days, the comparison was restricted to "moderate" and "severe" cases. It has already been stated that in patients treated with ampicillin, the temperature took longer to settle and, therefore, only those patients treated with chloramphenicol were considered. It was found that the mean

duration of pyrexia in patients who had a severe initial infection was significantly longer than in those who had only a moderate initial infection ($t = 2.44$ $P < 0.02$).

It might be expected that those patients who ate the initially infected meat would have a larger dose of organisms and possibly a more severe initial infection. When this was examined for those patients who ate on the 6th and 7th of May it was found that, of 26 patients, 21 were severely ill initially and 5 had a moderate initial infection. This was a higher proportion of severe cases than expected.

It was stated by Longchampt and Carbonel (1950) that patients who had a mild illness on admission were more likely to relapse than others, whereas Rowland (1961) found that patients who were severely ill on admission had a significantly higher relapse rate. In Aberdeen there were very significantly fewer patients than expected with a mild initial infection who relapsed ($\chi^2 = 22.08$, $P < 0.0005$).

It has been stated previously that typhoid patients who suffer a mild illness or are not ill at all may excrete typhoid bacilli for a long time (Section I). However, when convalescent excreters and other patients in Aberdeen were

compared for severity of the initial infection, it was found that very significantly fewer patients than expected with a mild initial infection continued to excrete typhoid bacilli during convalescence ($x^2 = 15.33$, $P < 0.0005$).

CONCLUSIONS

The Severity of the Initial Infection was shown to be related to several factors, thus:-

(a) Men were found to be less severely ill than women, but this was shown to be an effect of previous immunisation, since there was no difference in the severity of the illness between uninoculated males and females.

(b) Patients who were severely ill on admission to hospital took significantly longer to respond to treatment than patients who were only moderately ill.

(c) Patients who were severely ill on admission were significantly more likely to relapse than were other patients.

(d) Patients who were severely ill on admission were significantly more likely than other patients to become convalescent excreters.

It must be emphasised, however, that while it is

possible to compare the effects of different degrees of severity of the initial illness within one outbreak, no accurate comparisons can be made between different outbreaks until a satisfactory classification of the severity of the typhoid illness is universally agreed.

(v) Complications of Typhoid Fever

The abdominal complications of typhoid, namely melaena and bowel perforation, are unusual nowadays because of early hospitalisation and chloramphenicol therapy, but toxic effects are still sometimes seen, for example myocarditis and peripheral neuritis. There are also the results of immobilisation, namely thrombo-embolic and chest complications, which continue to occur in susceptible individuals.

The incidence of complications in Aberdeen is shown in Table 19. It may be seen that alopaecia during convalescence was observed more frequently than has previously been reported, probably because the patients were reviewed three months after discharge from hospital. In some children it amounted to almost total baldness, in other patients it was merely excessive hair-

TABLE 19

INCIDENCE OF COMPLICATIONS IN 469 TYPHOID PATIENTS

COMPLICATION	NUMBER	PERCENTAGE OF 469
DEATHS	3	0.6
CLINICAL RELAPSE	86	18.3
DEEP VENOUS THROMBOSIS	10	2.1
PULMONARY EMBOLISM	9	1.9
CARDIAC FAILURE	8	1.7
PERIPHERAL NEURITIS	8	1.7
PNEUMONIA	7	1.5
CHOLECYSTITIS	6	1.3
ARTHROPATHY	4	0.8
SUPERFICIAL PHLEBITIS	3	0.6
MYOCARDITIS	3	0.6
"PSYCHOSIS"	2	0.4
MYOCARDIAL INFARCTION	2	0.4
MELAENA	1	0.2
CEREBRAL INFARCTION	1	0.2
TYPHOID SKIN ULCER	1	0.2
SPINAL OSTEOMYELITIS	1	0.2
ALOPAECIA	220	46.9

:fall. In all patients healthy hair grew again within three months, and one bald man acquired a slight growth of new hair.

The incidence of other complications is similar to that reported in other outbreaks. Some of these complications will be considered in detail in this Section, and relapse and post-treatment pyrexia will be discussed in Section III.

(A) DEATH

There were 3 deaths, giving the very low mortality rate of 0.6%. Two of those who died were "poor-risk" patients, while the third was very ill at home for 14 days before she allowed a doctor to see her.

The details of these patients are, as follows:-

Patient No.264 was a frail woman of 60 who was admitted on the 8th day of illness. She lived alone and was toxic and very dehydrated on admission, with hepato-:splenomegaly; she also had a pronounced Parkinsonian tremor. She was given intravenous fluids and chloramphenicol, but collapsed 24 hours later: E.C.G. was suggestive of myocardial infarction, but she also had a blood urea of 150 mg.% which continued to rise. Despite stimulants and digoxin given intravenously, she died on the following day. No positive isolation of S. typhi was obtained, but she had S. typhi 'H' serum agglutinins at 1:400 dilution. A post-mortem was not performed.

Patient No.229 was also a slim woman of 60 who was admitted on the 14th day of illness when she was very toxic, dehydrated and delirious. She had been in bed with gastro-enteritis for 10 days, only rising to prepare food for her husband and brother who were also seriously ill! She had a positive clot culture on admission with serum H agglutinins to a titre of 1:50. She was given intravenous fluids for 5 days, with chloramphenicol 3 gm. per day for 3 days then 2 G. per day for 5 days and 1 G. per day for a further 7 days, the mean daily dose being 33 mg/Kg. body weight. Her temperature became normal on the 8th day of treatment. However, she suffered a severe relapse 6 days later with proved typhoid bacteraemia. She was given ampicillin 4G. per day but collapsed suddenly 3 days later and died.

At post-mortem, she was found to have had a left femoral vein thrombosis with bilateral pulmonary emboli. Typhoid bacilli were isolated from liver, spleen, gall-bladder, blood and intestine (first and second parts of ileum, and rectum).

Patient No.420 was a well-built man of 76 who was originally admitted to hospital because of a positive clot culture found when he was tested as a contact. His only symptoms at that time were of an acute bronchitis, although his blood still gave a positive culture after 6 days. Widal's reaction was negative except for S. paratyphi B 'O' agglutination to a titre of 1:100. His temperature responded within 3 days to chloramphenicol 2 G. per day and this was continued for 14 days to a total dose of 22 G. However, he developed mild congestive cardiac failure towards the end of treatment and, although this responded to diuretics he developed broncho-pneumonia a week later and died, despite antibiotic therapy. Post-mortem was not performed.

(B) MELAENA

The only patient to have serious abdominal complications with melaena was a boy of 11, Patient No.172, who was one of the first patients to be admitted. At that time, his 6th day of illness, he had both faeces and blood culture positive and a Widal test showed S. typhi 'H' antibodies at 1:1600 dilution and S. Paratyphi B 'O' antibodies at 1:100 dilution. He was very toxic, with delirium and dehydration, and responded only slowly to oral chloramphenicol: after 2 days this was changed to an intravenous infusion. On the following day he showed the classical sudden fall in temperature and rise in pulse associated with intestinal bleeding; his blood pressure dropped suddenly but was maintained with intravenous hydrocortisone. He continued to bleed intermittently for two days with a fall in haemoglobin to 60%, but with transfusion of 4 pints of blood his condition improved and his progress thereafter was uneventful.

(C) CHOLECYSTITIS

None of the 7 patients who had cholecystitis had a previous history of flatulent dyspepsia. All were between

the ages of 30 and 66. Six were women and two of them became convalescent carriers and will be discussed further in Section VII.

(D) PREGNANCY

A foetal death-rate of 60 - 80% was recorded in 60% pregnant women suffering from typhoid fever before the advent of chloramphenicol (Stevenson et al, 1951), but the rapid reduction in pyrexia with this drug has considerably reduced foetal mortality. However, Schaohter (1956) quoted three cases of neuro-psychiatric disorders in children whose mothers had typhoid during the 1st and 5th months of pregnancy.

Four patients during the Aberdeen outbreak were pregnant; one was at 12 weeks gestation, another at 16 weeks and a third, who was a symptomless excretor, was 32 weeks pregnant. All have since delivered normal healthy infants whose development to date appears to be normal. The fourth pregnant patient, No. 190, was admitted from the ante-natal clinic on the second day of illness, and was delivered of a normal healthy baby on the following day. The baby showed no antibodies in cord

blood, but this was not surprising since the mother's Widal reaction was also negative, although her blood and faeces cultures were positive. Her temperature fell slowly, reaching normal on the 9th day of treatment with chloramphenicol, the mean dosage being 32 mg. per Kg. body weight per day for 14 days, but she suffered a very severe relapse 10 days after the end of treatment. She was given a further 14 days of chloramphenicol in a dosage of 25 mg. per Kg. per day, to which her temperature responded after 2 days. She relapsed again 21 days after the end of the second course of treatment and was again treated with chloramphenicol for 14 days. She continued to excrete S. typhi for a further two months but finally cleared spontaneously.

This patient is interesting in that at the time of her first relapse, stool and blood culture showed S. typhi resistant to chloramphenicol, while a vaginal swab at the same time showed S. typhi sensitive to the same drug. She was allergic to ampicillin and treatment with chloramphenicol was, therefore, continued, to which she responded symptomatically. All further positive isolations showed organisms sensitive to chloramphenicol. The baby was well and developing normally when seen at the age of 9 months.

(E) ARTHROPATHY

There were four women who had painful joints with negative X-Ray findings. In two the shoulder joint was affected; one had a painful, swollen knee and the fourth had "tender toes", that is, painful, swollen metacarpo-:phalyngeal joints. All four resolved spontaneously.

(F) SOME UNUSUAL COMPLICATIONS

The last patient to be admitted to hospital, Patient No.535, was a man of 65 who ate fruit from the infected shop on 15th May, 1964 and had diarrhoea on the following day for 24 hours. Thereafter he was well until 10th July, 1964, when he had symptoms of cholangitis with fever and jaundice for 3 days. He remained "off colour" until 27th July, 1964, when he developed high fever and was admitted to hospital on 31st July. Clinically his condition resembled the late stages of typhoid fever and he had serum agglutinins to S. typhi 'H' at 1:1600 dilution, and to S. paratyphi B 'H' at 1:50 (he had been immunised in 1918); no 'O' antibodies were demonstrated.

He responded slowly to 14 days of chloramphenicol therapy but his temperature began to rise again 24 hours after cessation of treatment and on 20th August, 1964 blood culture was positive (on the seventh sub-culture). He responded well to treatment with tetracycline and was discharged from hospital on 21st September, 1964. Shortly afterwards he began to have backache which became progressively worse; X-Ray of spine on 10th December, 1964 revealed osteomyelitis in dorsal vertebrae 9 and 10. He was operated on on 29th December when resection of the 10th rib revealed some necrotic bone which, when cultured, gave a scanty growth of S. typhi. Convalescence was uneventful and he was discharged home on 26th March, 1965.

At no time were typhoid bacilli isolated from faeces

or urine in this patient. His serum agglutinins to S. typhi 'H' remained at 1:1600 with an occasional variation of one dilution, while S. typhi 'O' agglutination was negative until post-operatively when it rose to a dilution of 1:200. It is interesting to note that his level of serum Vi antibodies at the time of his re-admission and for a month before that was, at 1:640 dilution, one of the highest recorded in Aberdeen. Dr. E. S. Anderson (personal communication) has also observed the association of persistently high Vi agglutinin levels with typhoid infection of bone.

A second patient, No. 9, who gave a positive isolation of S. typhi from an unusual site was a woman of 75 with proved typhoid fever, who developed a superficial thrombo-phlebitis of her left calf on her 13th day in hospital. An ulcer developed over this area while she was still having chloramphenicol and a swab of the pus showed a profuse growth of S. typhi; the ulcer responded well to topical chloramphenicol.

The third patient with an unusual complication was a man of 43, Patient No. 455, who was admitted to hospital on 16th July, 1964 with proved typhoid fever. He had an uneventful stay in hospital except that his E.S.R. before discharge was 58 mm; he was asked to remain in hospital to have this investigated but was very anxious to go home. Two weeks later he had sudden severe left-sided chest pain which recurred a week later. He was treated at home with penicillin and streptomycin because of lobar pneumonia. A week later he had a third attack of left-sided pleural pain accompanied by rusty sputum, but he recovered sufficiently to return to work 3 weeks later. Then on 8th October, 1964 on his 120th day of illness, he was admitted to hospital because of recurrent fever with rigors and abdominal pain, and blood culture on 10th October, 1964 was positive for S. typhi. Chest X-Ray showed irregular left basal consolidation, and sputum culture revealed a heavy growth of B. coli, although no typhoid bacilli could be isolated. It seems very likely that such a late relapse was caused by reinfection from a focus in lung tissue which had been infarcted following a pulmonary embolus. Serum agglutination

to S. typhi 'H' remained at a dilution of 1:800 from the time of first discharge until March, 1965, and Vi agglutination on re-admission and since was to a dilution of 1:160; on 10th July, 1965, the chest lesion was improved but still showed a possible atelectactic patch.

There were 48 patients who suffered one or more complications(See Appendix II.49). There was no significant difference in the sex distribution of these and other patients, but very significantly more of them were aged 60 or over ($x^2 = 53.34$, $P < 0.0005$). This is to be expected, since the incidence of thrombo-embolic complications is usually higher in older patients, and a large proportion of the observed complications were of this nature. There was also a significant difference in the duration of pyrexia on initial treatment between these and other patients, both for severely and moderately ill cases ($t = 2.45$ $P < 0.02$ and $t = 2.76$ $P < 0.01$ respectively), although there was no significant difference in the severity of the initial infection or of the dosage and duration of initial treatment.

This, it would appear - as might be expected - that typhoid patients over the age of 60 who do not respond quickly to antibiotic treatment are more likely than other patients to suffer complications.

H. CONCLUSIONS

The Aberdeen typhoid outbreak of 1964 was remarkable epidemiologically, in that one can of meat produced in South America was presumed to infect approximately 500 persons in Aberdeen. The hospital control of the outbreak was greatly aided by the formation of a co-ordinating centre to communicate with general practitioners and medical officers of health. The death rate, at 0.6%, and the incidence of chronic carriers, at 1%, were both low.

The clinical features observed in this outbreak were, in the main, those of classical typhoid fever, but severe diarrhoea in the first week of illness was seen more frequently than is usual in typhoid fever. Bradycardia and leucopenia were rare.

Patients who had a severe initial typhoid infection were slower to respond to treatment than other patients and were more likely to relapse and to become convalescent excreters. Previous immunisation was found in general to mitigate the severity of the complete illness.

Complications occurred more often in older patients who were slow to respond to treatment. Abdominal complications were rare, but thrombo-embolic episodes accounted for approximately half of the complications which were observed.

SECTION III

THE TREATMENT OF TYPHOID FEVER

In this section, the modern treatment of acute typhoid fever is outlined and the treatment used in Aberdeen is described. The problems of the typhoid relapse, which is believed to be aggravated by present-day treatment, is examined, and a possible explanation of the effect of chloramphenicol on relapse is discussed.

The characteristics of the patients in Aberdeen who relapsed are outlined.

A. THE TREATMENT OF TYPHOID FEVER

Chloramphenicol is still undoubtedly the most effective drug in the treatment of acute typhoid fever. It greatly reduces the mortality rate and modifies the severity of the illness. However, it is not the ideal treatment, since the relapse-rate in typhoid fever has increased with the use of chloramphenicol (Woodward et al, 1948, Marmion 1952 and others). It also carries a small but grave risk of producing aplasia of the bone marrow (Hodgkinson, 1954). Smick et al.(1964) estimate this risk conservatively at 1:60,000. While these factors by no means outweigh the advantages of using chloramphenicol, a safer but equally effective drug would be preferable.

In 1961 a new antibiotic, ampicillin, was introduced (Rolinson and Stevens, 1961). It was found to be bactericidal to S. typhi in vitro and accordingly was used in the treatment of chronic carriers. Initially the drug was given for only 1 week (Trafford et al.1962), but Bullock (1963) found that only 3 of 7 carriers remained negative after treatment lasting for 12-21 days. Christie (1964) treated 8 chronic carriers with intra-muscular ampicillin for 1 week followed by 12 weeks of oral

treatment, combined with probenicid to inhibit elimination of the antibiotic by the kidneys (Walker and Hunter, 1951). In 7 of the carriers all specimens became clear immediately and were still negative a year later. The eighth carrier had a further course of treatment and the result was uncertain at the time of writing. In view of the success in most of these carriers, it was hoped that ampicillin would be successful in the treatment of the acute illness as it was not known to have any serious side-effects.

Comparison of the actions of chloramphenicol and ampicillin in acute typhoid and paratyphoid fevers (Scioli et al, 1964, Sleet et al, 1964) showed that ampicillin took approximately 6 days to reduce fever to normal, whereas chloramphenicol took only 3 days. Sensitivity reactions to ampicillin in the form of skin rashes were common but not serious, and it was felt that the latter was a useful drug in cases where chloramphenicol was contra-indicated. However, both Scioli et al,(1964) and Manriquez et al.(1965) observed that ampicillin did not always succeed in reducing the fever, and this would preclude its use in very severely ill patients.

Another new antibiotic, cephaloridine, was also shown

to be active in vitro against S. typhi (Muggleton et al, 1964). However, it was not found to be of value in the acute illness in 3 patients in Aberdeen (Walker, 1964).

Cortisone has also been used in the treatment of typhoid fever, both alone and in combination with chloramphenicol (Woodward et al, 1951, Watson 1957, Rowland 1961). Cortisone has a non-specific anti-inflammatory action and increases the patient's resistance to stress. It causes an earlier fall in temperature and is of value in very toxic patients, but it also increases the danger of intestinal haemorrhage and perforation., (Woodward et al.1964). Woodward considered that its use alone was not justified and that it was safer to reserve the use of steroids with chloramphenicol for patients who were severely toxic and shocked.

Thus, chloramphenicol remains the drug of choice in the treatment of acute typhoid fever.

B. THE TREATMENT OF TYPHOID FEVER IN ABERDEEN

(i) The Treatment of the Initial Illness

Of 454 patients who received antibiotic treatment, 390

had chloramphenicol initially. The dosage of this varied with the consultant in charge of each ward, but all treatments were continued for at least 14 days. The main schedules of treatment in adults were:-

(1) 500 mg. 6-hourly for 7 days, then 250 mg. 6-hourly for 7 days, to a total dose of 21 G.

(2) 500 mg. 4-hourly for 2 days, 500 mg. 6-hourly for 5 days, then 250 mg. 6-hourly for 7 days, to a total dose of 23 G.

(3) 4 G. loading dose, followed by 500 mg. 4-hourly until the temperature fell below 100°F., then 500 mg. 6-hourly for 7 days; then 500 mg. 8-hourly to a total of about 14 days - total dose 26 - 40 G.

Except in a few cases of severe toxicity, all treatment was given orally. A few cases had intravenous or intramuscular drugs initially.

Six adults who were not severely ill were treated initially with ampicillin in a dosage of 1 G. 6-hourly for 14 days. Other 3 adults were given cephaloridine 1 G. 12-hourly initially, but all three had to have the treatment changed to chloramphenicol on the third day because of failure to respond (Walker, 1964). Figures 9, 10 and 11 show typical temperature

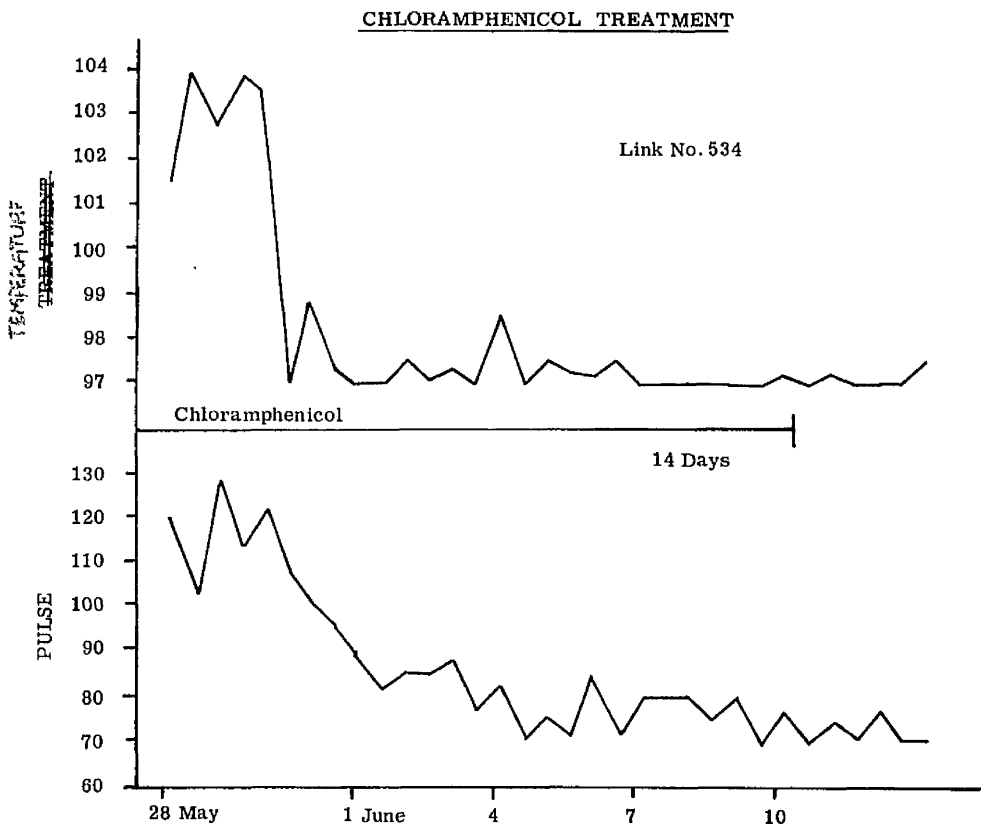


Fig. 9 - Temperature Chart of a Patient treated initially with Chloramphenicol.

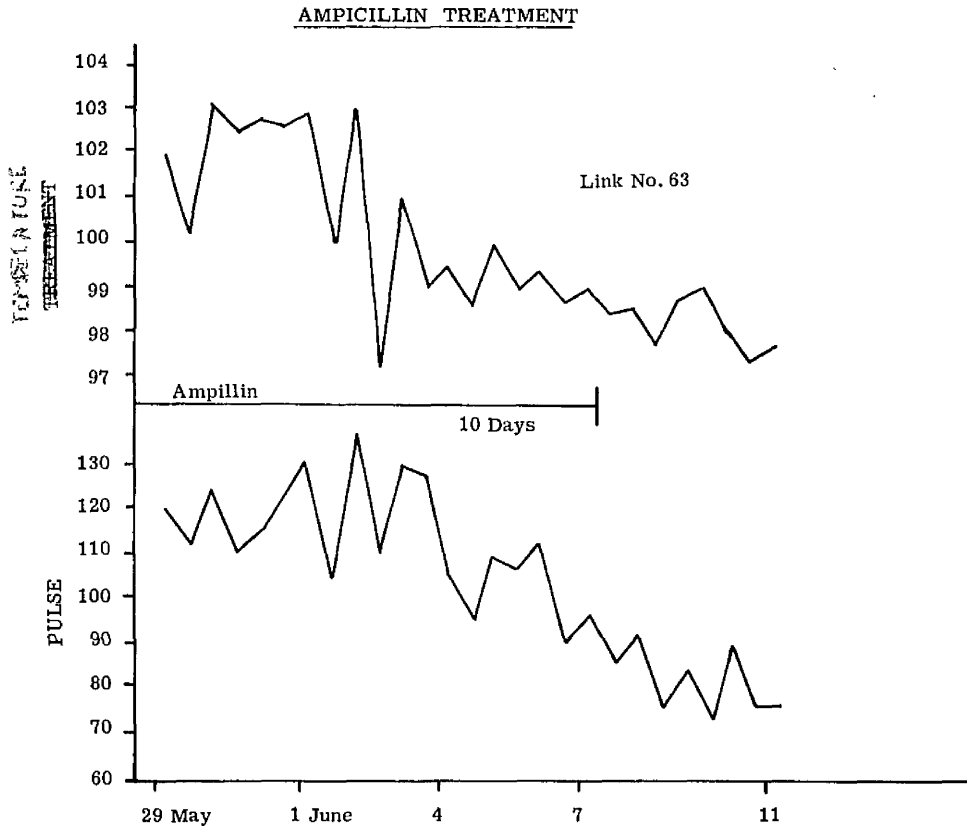


Fig. 10 - Temperature Chart of a Patient treated initially with Ampicillin.

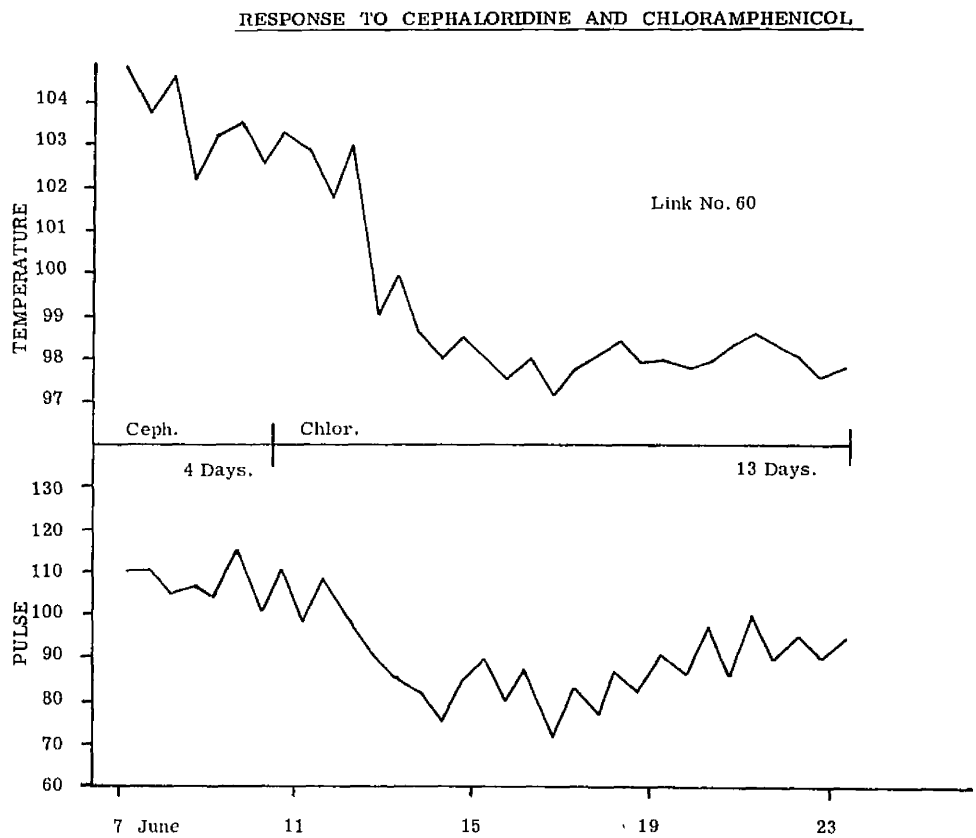


Fig. 11 - Temperature Chart of a Patient treated initially with Cephaloridine.

charts of patients treated initially with chloramphenicol, ampicillin and cephaloridine respectively.

In children, 4 different schemes of treatment were given for the initial illness:-

(1) Chloramphenicol 250 mg. 6-hourly for at least 14 days for children aged 6 - 12 years, and half that dose for children under 6 years.

(2) Ampicillin 250 mg. 6-hourly for at least 14 days or 125 mg. 6-hourly in younger children.

(3) Chloramphenicol for approximately 7 days, followed by ampicillin for approximately 7 days in the same dosages as (1) and (2) above.

(4) Ampicillin followed by chloramphenicol in the same pattern as (3) above.

Details of all these treatments are shown in Table 20. Ancillary treatments used were steroids, given to 5 patients because of extreme toxicity, intravenous fluids given to 3 because of dehydration, and blood transfusion to one child because of melaena.

(ii) The Treatment of Relapse

Patients who relapsed or were re-treated because of fever had a variety of treatments:-

TABLE 20

DETAILS OF INITIAL TREATMENT USED IN ABERDEEN TYPHOID OUTBREAK, 1964

TREATMENT	NUMBER	MEAN DAILY DOSE (MG/KG. BODY WEIGHT)	MEAN DURATION OF TREATMENT (DAYS)	MEAN DURATION OF ILLNESS BEFORE TREATMENT (DAYS)
CHLORAMPHENICOL				
ADULTS	352	29	13.9	7.7
CHILDREN	58	32	13.9	6.5
AMPICILLIN				
ADULTS	6	53	12.8	17.3
CHILDREN	25	46	15.0	6.3
CHLORAMPHENICOL FOLLOWED BY AMPICILLIN				
ADULTS	4	C.30;A.21	C.9.7;A.5.7	8.0
CHILDREN	12	C.37;A.43	C.7.3;A.7.3	6.8
AMPICILLIN FOLLOWED BY CHLORAMPHENICOL				
ADULTS	4	A.48;C.38	A.8.5;C.9.3	9.3
CHILDREN	10	A.37;C.38	A.8.6;C.8.6	5.5
CEPHALORIDINE FOLLOWED BY CHLORAMPHENICOL				
ADULTS	3	CEPH.33 C. 29	CEPH. 3.0 C. 13.7	9.3

TABLE 21

TREATMENT OF PATIENTS WHO RELAPSED

ABERDEEN TYPHOID OUTBREAK, 1964

DRUG	DAILY DOSE (G)	NUMBER TREATED	MEAN DURATION OF PYREXIA ON TREATMENT (DAYS)	RANGE OF PYREXIA ON TREATMENT (DAYS)
CHLORAMPHENICOL	2-3	24	3.8	1 - 6
CHLORAMPHENICOL WITH CHLORTETRACYCLINE	1 / 1	11	3.8	2 - 6
AMPICILLIN	4	15	7.0	3 -10
DO.	8	9	5.5	3 - 8

TABLE 22

ASSESSMENT OF TREATMENTS

ABERDEEN TYPHOID OUTBREAK, 1964

TREATMENT	NUMBER TREATED	MEAN DURATION OF PYREXIA ON TREATMENT (DAYS)	RELAPSE RATE	CONVALESCENT EXCRETER RATE
CHLORAMPHENICOL				
ADULTS				
DOSAGE: 15-24 MG/KG	100	4.4	16.0	25.0
25-34 "	172	4.4	22.7	22.1
35+ "	60	4.0	23.3	23.3
CHLOR. - ADULTS :	332	4.4	20.8	24.1
- CHILDREN :	58	4.4	19.0	36.2
CHILDREN				
AMPICILLIN	25	8.3	0.0	56.0
CHLOR. + AMP.	12	3.7	25.0	41.7
AMP. + CHLOR.	10	12.6	30.0	50.0

* THESE FIGURES INCLUDE ONLY THOSE PATIENTS WHO HAD A SINGLE COURSE OF TREATMENT DURING THE ACUTE ILLNESS.

(1) chloramphenicol for 10 days in dosages varying from 500 mg. 4-hourly to 250 mg. 6-hourly (33 patients)

(2) chloramphenicol and chlortetracycline together for 10 days in a dosage of 250 mg. of each 6-hourly (11 patients)

(3) cephaloridine 1 G. 12-hourly for 14 days (2 patients)

(4) methacycline (Rondomycin) 300 mg. 6-hourly for 10 days. (8 patients)

(5) ampicillin 1 G. 6-hourly or 2 G. 6-hourly for 10 days (30 patients)

The effects of some of these treatments on pyrexia are shown in Table 21.

(iii) Response to Treatments

The effects of different drugs and schedules of treatment were compared, where possible, on the basis of:

(1) the duration of pyrexia on treatment

(2) the incidence of relapse after treatment

(3) the incidence of the excreter state during convalescence.

The details of these effects are shown in Table 22.

With regard to the treatment of the initial illness

in adults, it was not possible to compare the effects of different regimes of chloramphenicol treatment, since the resultant individual dosage per kgm. body-weight varied considerably. However, the effect of different daily dosages per kgm. body-weight were compared. No significant differences were found in the duration of pyrexia or in the relapse-rate, although there was a trend for the incidence of relapse to increase with increasing daily dosage of chloramphenicol. This was thought to be because patients who were extremely ill on admission were often given a higher dosage of chloramphenicol and these patients were more likely than other patients to relapse. There was no difference in the incidence of convalescent excreters in the three dosage groups.

There was no difference in the effect of chloramphenicol in adults and in children. Since adults who were given treatments other than chloramphenicol alone were selected either because of a milder degree of illness or because of allergy, it was not possible to compare the effects of these treatments in adults. However, when ampicillin and chloramphenicol were compared as initial treatment in children, it was found that there was a very significantly longer period of pyrexia in children who

were given ampicillin ($t = 3.98$, $P < 0.01$) with a mean of 8.3 days, as opposed to 4.4 on chloramphenicol. However, the dosage of ampicillin was probably inadequate; patients treated with ampicillin 2 G. 6-hourly during relapse responded more quickly than those who had only 1 G. 6-hourly, although the difference was not significant. (Table 21).

The relapse-rate in children treated with chloramphenicol was 19.0%. None of the 25 children treated with ampicillin alone relapsed, although there was no difference between the two groups in severity of the initial infection. The incidence of convalescent excreters did not differ significantly between the two treatment groups.

When the mixed treatments in children were compared, those children who had ampicillin first had significantly longer mean duration of pyrexia than those who had chloramphenicol first ($t = 5.86$, $P < 0.01$), that is 12.6 days as compared with 3.7 days. There was no significant difference between these two groups in the incidence of relapse or convalescent excreters.

These findings suggest that ampicillin is slower than chloramphenicol in reducing the fever and toxicity of typhoid fever, but that patients who receive no chloramphenicol are less

likely to relapse. A further point of interest is that 7 patients relapsed between the second and fourth days of treatment with ampicillin, 1 G. 6-hourly, given because of convalescent excretion. Closer examination of the temperature charts of these patients showed that in 4 of them the temperature began to rise before ampicillin therapy was commenced. In the other 3 who relapsed on the fourth day of treatment, the temperature rose more abruptly than usual, reaching 101 - 102°F. from normal within 8 hours. It seems, therefore, that ampicillin given initially in the dosage used in Aberdeen will make the occurrence of relapse less likely than when chloramphenicol is used, but that in the dosage used here it will not forestall the onset of relapse if given later; indeed, it is possible that it may precipitate the onset of symptoms.

The object of any treatment is to restore the patient to "normal" health as quickly and as efficiently as possible. Such treatment should not be detrimental to the patient's future health. Chloramphenicol may expose the patient to the risk of an illness prolonged by a relapse and to a further risk of bone-marrow aplasia. It is debatable whether its more rapid initial action justifies its use in place of ampicillin, which does not

appear to expose the patient to these risks. Further, it was observed that, although ampicillin was less effective in reducing pyrexia, there was little difference between the drugs in the time taken to produce symptomatic relief. It is possible, therefore, that if a patient is critically ill or is known to be sensitive to penicillin chloramphenicol remains the drug of choice, but that in a less severely ill patient, and in one in whom treatment is initiated early in the illness, ampicillin should be given, and only if it fails to produce relief of symptoms and pyrexia should chloramphenicol be used.

It may be seen from Table 21 that chloramphenicol alone and chloramphenicol combined with chlortetracycline were equally successful in the treatment of relapse. Since the latter treatment was not used initially it was not possible to assess its effect on the incidence of relapse or persistent excretion.

Cephaloridine and methacycline were given to patients who were allergic to penicillin and who had previously had large doses of chloramphenicol; it was difficult to assess whether the subsequent slow fall in temperature was due to the drugs or was the natural course of the illness.

(iv) Some Side-Effects of Treatment

1. Chloramphenicol - the most common side-effects of chloramphenicol therapy were glossitis and pharyngitis, which were seen severally or together in a total of 51 patients (14%). Both usually appeared on the 3rd or 4th day of treatment and continued for a day or two after treatment stopped. In 4 ill patients severe monilial infection of the mouth was seen, although this may have been partly due to typhoid as well as to treatment. Dysphagia and nausea were common in a mild degree, and vomiting occurred in 2 patients. Severe urticarial drug rash was seen in one man on the 8th day of treatment, and 6 other patients had maculo-papular rashes occurring about the same time.

One child developed neutropaenia 3 weeks after the end of a 14 days' course of chloramphenicol and 2 days after the end of a 10 days' course of ampicillin 3 G. daily given because of relapse. She had an associated tonsillar mycosis and white cell count showed only 12% neutrophil polymorphs. However, this rose spontaneously over the next 10 days to a normal level.

Up until a year after the end of treatment, no bone-marrow aplasia was detected at follow-up examination.

(iv) (Contd.)

2. Ampicillin - the most common side-effect of ampicillin therapy was allergic skin reactions which varied from gross generalised urticaria to a mild morbilliform rash which disappeared after a few days even when treatment was continued. Some unusual forms of rash were seen, for example, one closely resembled Campbell de Morgan's spots, while an other presented as blisters which appeared half-an-hour after administration of the drug and lasted for 3 - 4 hours. Several patients with allergic reactions were at first thought to have recurrent rose spots. In all, 39 of 198 patients who received ampicillin for one reason or another showed sensitivity rashes which first appeared from the 1st to the 8th day of treatment. Diarrhoea occurred in 11 patients and was severe in 3 of them, and several patients complained of depression while taking ampicillin.

An interesting example of a "toxic crisis" occurred in Patient No.190, a woman of 26, whose temperature chart is shown in Figure 12. On the second day of a course of ampicillin 1 G. 6-hourly, given because of convalescent excretion, she relapsed. Ampicillin was continued for a further 60 hours but her condition worsened; her temperature reached 105°F. and she was given 4 G. of chloramphenicol, half intramuscularly and half orally. She was given 1.5 G. of chloramphenicol orally on the following morning but vomited after it and the dose was not repeated. By 12.30 p.m. she was again very toxic; at that point blood and stool cultures of two days previously were reported as showing S. typhi resistant to chloramphenicol and she

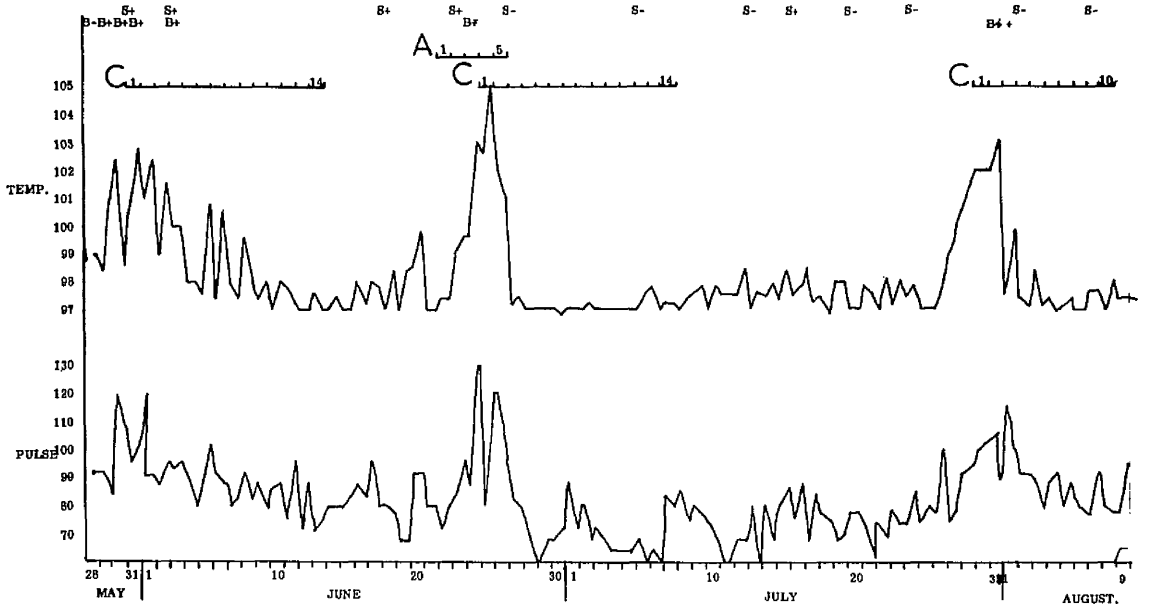


Fig. 12 - Temperature Chart of a Patient who suffered a "toxic crisis" on relapse.

(iv) (Contd.)

2. Ampicillin (Contd.)

was given ampicillin, 1 G. intravenously and 1 G. intramuscularly. One-and-a-half hours later she collapsed and was extremely shocked; she responded slowly to intravenous hydrocortisone, 400 mg. in divided doses over 8 hours, with chloramphenicol 2 G. intravenously and 2 G. intramuscularly. By the next day her blood pressure had returned to normal and her temperature had dropped suddenly to 97.2°F., where it remained for 10 days.

The crisis in this patient was unlikely to have been due to chloramphenicol since the last dose was given 20 hours previously. It is much more probable that the intravenous dose of ampicillin given 1½ hours prior to collapse killed large numbers of bacteria simultaneously, releasing a massive dose of endotoxin and thereby increasing the level of toxicity sufficiently to produce shock. The picture is, however, clouded by the fact that this patient was allergic to ampicillin and on the day of collapse developed a marked skin eruption due to her previous three days' treatment. Nonetheless it serves as a reminder of the potential danger of large "loading doses" of any bactericide when bacteraemia exists.

Patient No.84, a woman of 30, illustrates clearly the fact that antibiotic therapy is not always effective in typhoid fever. She was admitted on the 4th day of illness and was treated initially with 500 mg. chloramphenicol 6-hourly for 7 days followed by 250 mg. 6-hourly for 7 days. Her temperature fell to normal on the 7th day of treatment but rose again on the last day; blood culture was negative but she was re-treated 6 days later with ampicillin 1 G. 6-hourly for a further

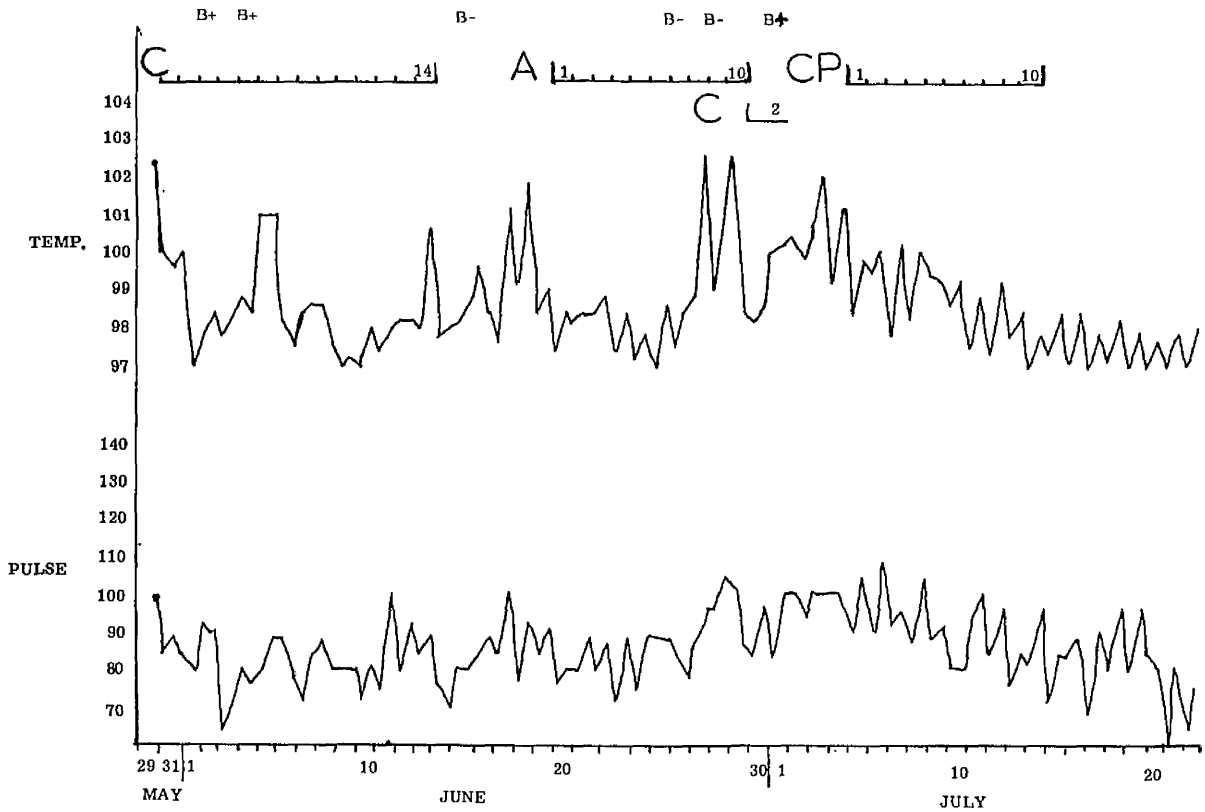


Fig. 13 - Temperature Chart of a Patient who did not respond to Antibiotic Treatment.

(iv) (Contd.)

2. Ampicillin (Contd.)

10 days. On the 8th day of this treatment she relapsed; blood culture was negative but became positive two days after cessation of ampicillin, by which time she had had two days of treatment with chloramphenicol and chlortetracycline in a dosage of 250 mg. of each 6-hourly. She was very ill at this time and also developed both a drug sensitivity rash and a severe monilial throat infection. Treatment was changed to cephaloridine 500 mg. 6-hourly with probenecid 500 mg. 12-hourly, both of which were continued for 10 days. Her temperature became normal on the 9th day of this drug (her 49th day of illness). Her convalescence thereafter was uneventful except for a single positive faeces specimen a month later. Unfortunately her serology was assayed only on admission and on discharge; on both occasions she had only S. typhi 'H' agglutinins at 1:50 dilution, although a month after discharge she had S. typhi 'O' agglutinins at 1:320 dilution. Her temperature chart (Fig. 13) closely resembles that of a case of untreated typhoid fever.

CONCLUSIONS

Chloramphenicol usually produces a rapid reduction of pyrexia in typhoid fever and for that reason is still the drug of choice in severe cases. However, it appears from the incidence of relapse which occurred in Aberdeen that ampicillin is less likely to cause a relapse. It is suggested that in patients who are not critically ill and in particular in patients who are treated early in the illness, ampicillin might be given in order not to increase the chances of a subsequent relapse.

The main side-effect of ampicillin is drug sensitivity, but this is less dangerous than the possibility, however remote, of bone-marrow aplasia following chloramphenicol therapy. The precise dosage of ampicillin which is most effective is not yet certain, but loading doses should be avoided because of the danger of producing shock.

C. THE PROBLEM OF RELAPSE IN TYPHOID FEVER TREATED WITH CHLORAMPHENICOL

(i) Incidence of Relapse

The incidence of relapse in untreated typhoid fever usually falls between 3.8% (Lantin et al.1963) and 14% (Hickstep 1962). In contrast, the incidence in chloramphenicol-treated typhoid is frequently about 20% (Woodward et al.1964) and may be as high as 58% (Hill et al.1950). It is true that the decrease in mortality rate which has resulted from the use of chloramphenicol gives scope for a higher rate of relapse, and furthermore the definition of a "relapse" is by no means uniform in different outbreaks. Seidler (1961) suggested that many so-called relapses after chloramphenicol were merely recrudescences of fever which was suppressed during the administra-

:tion of the drug. He compared the relapse rate in 3 groups of approximately 500 patients each, one untreated, one given short courses of chloramphenicol, and the third given the drug for 2 weeks. Of these, the middle group had a relapse rate of 10% as opposed to rates of about 6% in each of the other 2 groups. Seidler studied the case-records of patients who relapsed, and claimed that the relapse rate of the middle group was fallacious since many of these recorded relapses were not true relapses but merely showed an interruption of the expected temperature curve. However, while it is true that a universally agreed definition of a relapse would be of value, neither this disparity nor a lower mortality rate can entirely account for the higher incidence of relapse which has been recorded since the introduction of chloramphenicol therapy.

(ii) Factors which affect Relapse

The wide variation in the duration and intensity of the treatment used by different clinicians in their search for the regime least likely to cause relapse makes comparison of results difficult. (See Table 23). However, certain factors emerge as having a definite influence on the incidence of relapse. These are:-

1. The duration of treatment
2. The timing of the treatment

TABLE 23

RELAPSE RATES IN CHLORAMPHENICOL-TREATED TYPHOID FEVER QUOTED BY VARIOUS CLINICIANS

SOURCE	YEAR	NUMBER OF CASES	DAYS OF ILLNESS BEFORE TREATMENT	TREATMENT		DAYS OF PYREXIA ON TREATMENT	T-RELAPSE INTERVAL (DAYS)	DAY OF ILLNESS ON RELAPSE	RELAPSE RATE %	REMARKS
				DOSAGE (TOTAL OR DAILY)	DURATION OF TREATMENT (DAYS)					
WOODWARD ET AL.	1948	10	9.5	19.1 G	8.1	3.5	12	30	20.0	
SMADEL ET AL.	1949	13	13.5	20.0 G	6.9	)	11	32	53.8	
		19	13.7	25.7 G	11.2	) 4.2	-	-	-	
		12	20.8	32.8 G	18.0	)				
HILL ET AL.	1950	21	9.6	31.2 G	9.7	4.0	15	35	57	
MARMION	1952	47	)	34-38 G	14	3.9	)		18.2	
		34	) ?	34-38 G	14	5.3	) 11	?	17.6	T.A.B. FOR FIRST 10 DAYS.
		97	)	30 G	) INTERRUPTED	3.9	)		42.3	
		21	)	30 G	) 5-7-7	5.3	)		4.8	TAB FOR 1ST 10 DAYS
JOHN AND VINAYAGAM	1952	20	10	19 G	INTERRUPTED 6-5-6	) 4.0)	11	?	5.0	
		17	8	22 G	10	) 4.0	7		41.0	
EL RAMLI	1953	289	)	) 25 MG.	4-7	)			26.3	)
		)	)	)	INTERRUPTED	) 3.7	?	?		) 80%
		58	) 13.7	) PER	4-7-7	)			13.8	) WERE CHILDREN
		51	)	) KG.	16	)			3.9	)
WATSON	1957	300	> 7	c.21 G	14-19	4.0	?	?	6.0	
ROWLANDS	1961	78		60 MG/KG	5	)			11.5	
		90	?	30 "	10	) 4.8	?	?	3.3	
		83		30 "	5	)			20.5	
		89		15 "	10	)			12.4	
HUCKSTEP	1962	80		12-20 G	6-10				41.0	
		39		22-36 G	11-18				28.0	
		22	?	12-20 G	6-10	?		?	18.0	FOLLOWED BY T.A.B.
		10		22-36 G	11-18				10.0	FOLLOWED BY T.A.B.
LANTIN	1963	251	15.4	18 G	10	4.8		31	11.1	
FOURRIER ET AL.	1963	1,050	< 7	c.20 G	< 10	)			20.0	
					INTERRUPTED	) ?				
				34-38 G	14-5-5	)			1.0	

3. The level of antibody response before treatment.
4. The addition of vaccine therapy.
5. The severity of illness before treatment.

1. The Duration of Treatment

Smadel et al.(1949) were first to suggest that the duration of treatment affected the relapse rate. They stated that "chloramphenicol should be administered in adequate amounts for more than 8 days ..... there appears to be little advantage in continuing treatment for more than 14 days." They based this statement on the relapse rates which they observed after varying lengths of treatment. When chloramphenicol was given for 7 days the relapse rate was 54%, whereas after 11 or 18 days' treatment there were no cases of relapse. Woodward et al.(1954) summarised the results of several observers and stated that treatment for less than 10 days usually caused a relapse rate of about 20%. It seems clear that the highest relapse rates occur when chloramphenicol is given for less than one week (Smadel et al. 1949, Pokrovski and Bulkina 1960), and most investigators are now agreed that treatment should be continued for at least 14 days (El. Ramli 1953, Watson 1957, Huckstep 1962). However, even this length of treatment does not obviate relapse. It was

suggested that if chloramphenicol was given for four to six weeks continuously, that is, to cover the expected duration of the disease, relapse would not occur (Matteucci et al. 1951) but this regime was not wholly successful. Woodward et al. (1954) described a case to whom chloramphenicol was given from the third to the sixty-third day of disease and relapse occurred fifteen days later.

Several workers have advocated a schedule of interrupted treatment, that is, treatment continuing for 2 - 10 days after the temperature becomes normal followed by an interval of 5 - 8 days with no treatment, followed by a second course of chloramphenicol for 5 - 10 days. (Marmion 1952, John & Vinayagan 1952, El. Ramli 1953, Fourrier and Rocchicioli 1963, Forbes 1963). Woodward et al.(1954) suggested a further rest period of eight days followed by a third course of treatment for 5 days. It is thought that interrupted therapy allows for treatment at the period when relapse usually occurs, that is, 7 to 15 days after the end of the initial treatment. The relapse rate on this regime has varied from 1% (Fourrier and Rocchicioli 1963) to 42% (Marmion 1952). The chief difference between their respective schedules of treatment was in the first course of each: Marmion continued treatment for only 2 days after the

temperature was normal, whereas Fourrier continued it for 8 days.

This type of treatment has not been readily adopted because of the belief that interrupted dosage of chloramphenicol is more liable to cause aplasia of the bone-marrow than is continuous treatment (Sharp 1963). A recent trial of different daily dosages of chloramphenicol has suggested, however, that toxic bone-marrow depression is an inherent property of the drug, although it may be aggravated by individual sensitivity, and that it usually ceases on withdrawal of the drug. If this is so, interrupted dosage is no greater a source of danger than prolonged therapy (Scott et al. 1965)

The total duration of treatment appears to be less important in preventing relapse than the duration of treatment after the patient becomes afebrile. In patients on the same scheme of treatment, those who relapse have been shown to have a longer period of pyrexia on treatment (Rowland 1961) and, therefore, a shorter period of treatment while afebrile. However, as suggested earlier, this may be merely a reflection of the severity of the initial illness.

It seems also that the total dosage of chloramphenicol is not as important as the duration of time over which it is

given (Rowland 1961, Woodward et al.1964). The dosage recommended by most clinicians (Woodward et al.1954, Forbes 1963) is 50 mg. per kg. body-weight per day, in divided doses. The drug is usually given at 4-, 5- or 8-hourly intervals, although El Ramli (1953) suggested that 12-hourly administration is equally effective and causes less disturbance to the patient.

Thus, on the basis of these observations in man, all that may be stated with certainty about the duration of chloramphenicol therapy and its effect on the incidence of relapse is that treatment for less than 2 weeks is more likely to produce a higher rate of relapse. It is not yet possible to state that any one regime of treatment may be used in the knowledge that it will cause few patients to relapse. It is prudent to remember that the statement made by Marmion (1952) is still true, namely that an inherent quality of the infecting organism plays an important part in determining the relapse incidence in a given outbreak, and as this factor is not at present assessable, comparisons between different outbreaks are not valid.

2. The Timing of Treatment

3. The Level of Antibody Response before Treatment

Since these two factors are thought to be inter-:related, they will be dincussed together.

In 1950, Longchampt and Carbonel observed that typhoid patients in whom chloramphenicol therapy commenced in the first week of illness, were more likely to relapse than those in whom treatment was started later in the illness. Marmion (1952) confirmed this finding. He recorded relapse rates of 36.9, 25.5 and 19.7 per cent in patients in whom treatment was initiated in the first, second and third weeks of illness respectively. Marmion suggested that chloramphenicol might interfere with the production of immunity. In the following year Seeliger and Vorlaender found that chloramphenicol interfered with the normal production of 'O' antibodies. El Rooby and Gohar (1956) took this further and showed that chloramphenicol did not affect anti-:body production in persons who were given T.A.B. vaccine, that is, killed organisms, but that in typhoid patients it caused an increased rate of fall in serum antibody levels which was most marked when treatment started before the tenth day of illness. This fall occurred in both 'H' and 'O' serum antibodies, but was greater in the latter.

Kostic (1963) in 144 typhoid cases given chloramphenicol for 14 days made the following observations:-

(i) 'H' antibodies are not greatly affected by the administration of chloramphenicol, but 'O' antibodies are markedly decreased.

(ii) Chloramphenicol therapy started on the 1st and 2nd days of illness prevents the formation of 'O' antibodies.

(iii) Chloramphenicol therapy started on the 4th and 5th days of illness causes a slower and poorer rise in serum antibody levels than is usual.

(iv) Chloramphenicol therapy started on the 6th and 7th days of illness causes a more rapid disappearance of the 'O' antibodies already developed.

(v) These effects are even more obvious if other antibiotics have been administered before chloramphenicol therapy is initiated. They are also more marked if cortisone is given concurrently.

It is now generally agreed that chloramphenicol given early in the illness interferes with the production of immunity, that is, of the antibody to the pathogenic 'O' antigen. It is also thought, as Marmion suggested, that this diminution in antibody production makes relapse more likely (Lantin et al. 1963). There are, however, variations between different observers and different outbreaks. Rowland (1961) found that

the relapse rate did not vary with the timing of treatment, although he did not state what range of times he compared, and Woodward et al.(1954) observed several patients who relapsed in the face of high levels of circulating antibody.

4. The addition of vaccine therapy

Marmion (1952) gave T.A.B. vaccine, 0.02 ml. subcutaneously on each of the first 10 consecutive days of two different regimes of chloramphenicol treatment. The first was a continuous course of 25 - 30 grams of chloramphenicol over a period of about 9 days, the second an interrupted course of about 5 days' initial treatment, followed by 6 days' further treatment after an interval of a week. He found that in 81 patients given the continuous course the relapse rate (18%) was not affected by the addition of vaccine, whereas in 118 men given the interrupted course the relapse rate was only 4.8% in those who were given vaccine as opposed to 42.3% in those who were not. In the interrupted regime vaccine was given for 3 - 5 days after the withdrawal of chloramphenicol. Marmion concluded that the addition of vaccine should be effective in reducing the relapse rate, but that its action of stimulating antibody production was inhibited in the continuous course because chloramphenicol was given at the same time.

Huckstep (1962) gave 46 patients who had different regimes of chloramphenicol therapy a single dose of 0.25 - 0.5 ml. T.A.B. vaccine either between treatments, if the regime was interrupted, or immediately following a continuous course. He found that whatever the regime used, the relapse rate was more than halved by the addition of vaccine.

5. Severity of Illness before treatment

Various opinions have been expressed on the effect, if any, of the severity of illness on the relapse rate. Longchampt and Carbonel (1950) stated that relapse in chloramphenicol-treated cases more commonly followed a mild infection than a severe one. Maxmion (1952) denied any significant effect of the severity of the initial illness on the incidence of relapse, but he did not define "severity". Rowland (1961) who based his classification of "severity" largely on clinical impression, stated that cases of severe initial infection were more likely to relapse. Rowland also found that patients with a longer duration of pyrexia on initial treatment were more likely to relapse. This agrees with the finding in Aberdeen that the duration of pyrexia was greater in severely ill patients who relapsed.

DISCUSSION

It would appear, therefore, that the occurrence of a relapse in typhoid fever is influenced by the timing and duration of chloramphenicol therapy, by the presence or absence of circulating antibody, and by the severity of the initial attack. What, then, is the inter-relationship of these factors, and what is the mechanism of relapse?

It has been stated in Section I that in the natural course of typhoid infection in man the bacteria are taken up from the tissues and blood stream by phagocytic cells. Once inside the cell, they may:

(i) be destroyed
(ii) remain static
(iii) continue to multiply
(iv) be egested

The outcome is influenced by peculiarities of the organism, of the phagocyte and of the environment. In the main these influences are the resistance of the bacteria to destruction, the competence of the phagocyte, and the presence or absence of anti-body. The bacteria may multiply faster than the phagocytic cell is able to destroy them or than antibody can be produced, in which case the patient may die. On the other hand, the

bacteria may be destroyed mainly by phagocytes and antibody, and the acute illness will then subside.

The decrease in the number of live bacteria, both in untreated and in chloramphenicol-treated typhoid fever, is a gradual process. Marmion (1952) found bacteræmia late in convalescence when the patient was completely afebrile. Watson (1957) isolated S. typhi from clot cultures as late as the 17th day of treatment with chloramphenicol, again when the patients were afebrile. Watson believed that the blood stream was frequently re-invaded by bacteria from the tissues during the course of the illness and that, if such re-invasion by "tissue forms" of bacteria occurred to a sufficient extent, it would overcome the effect of circulating antibody and cause a clinical relapse. Furthermore, as the bacteria decrease in number during the patient's recovery, the antigenic stimulus is removed and by the time that relapse usually occurs the level of antibody has begun to fall and the patient is more susceptible to re-infection of the blood stream from foci in the tissues.

If this is the mechanism of relapse, some bacteria must survive and multiply in the tissues. It has been stated already that S. typhi may multiply within phagocytic cells, either because of the virulence or "resistance" of the bacteria, or

perhaps because the cell is incompetent.

It is also known that intracellular bacteria are protected from the action of humoral bacteriocides, including antibody (Rous and Jones 1916). Such bacteria may survive for some days or longer until they are released either when the cell dies naturally, or when they overpower it, or if they are ejected by a viable cell. It is quite likely that, of a large number of bacteria ingested simultaneously by phagocytes at the time of the initial infection, sufficient of those which survive will be released after an approximately equal length of time and, in favourable circumstances, cause a relapse.

What, then, is the action of chloramphenicol that it not only does not prevent the survival of some bacteria but appears to potentiate it?

The action of chloramphenicol is primarily bacteriostatic. By arresting the growth of bacteria it reduces the quantity of antigenic material available to stimulate antibody production. Watson (1957) believed that chloramphenicol also acted by increasing the rate of uptake of bacteria by phagocytic cells in the same way as streptomycin sensitises tubercle bacilli to phagocytosis (Linz 1953). This hypothesis is supported by the findings of Hopps, Smadel et al. in 1961 (See Figure 14.). In a

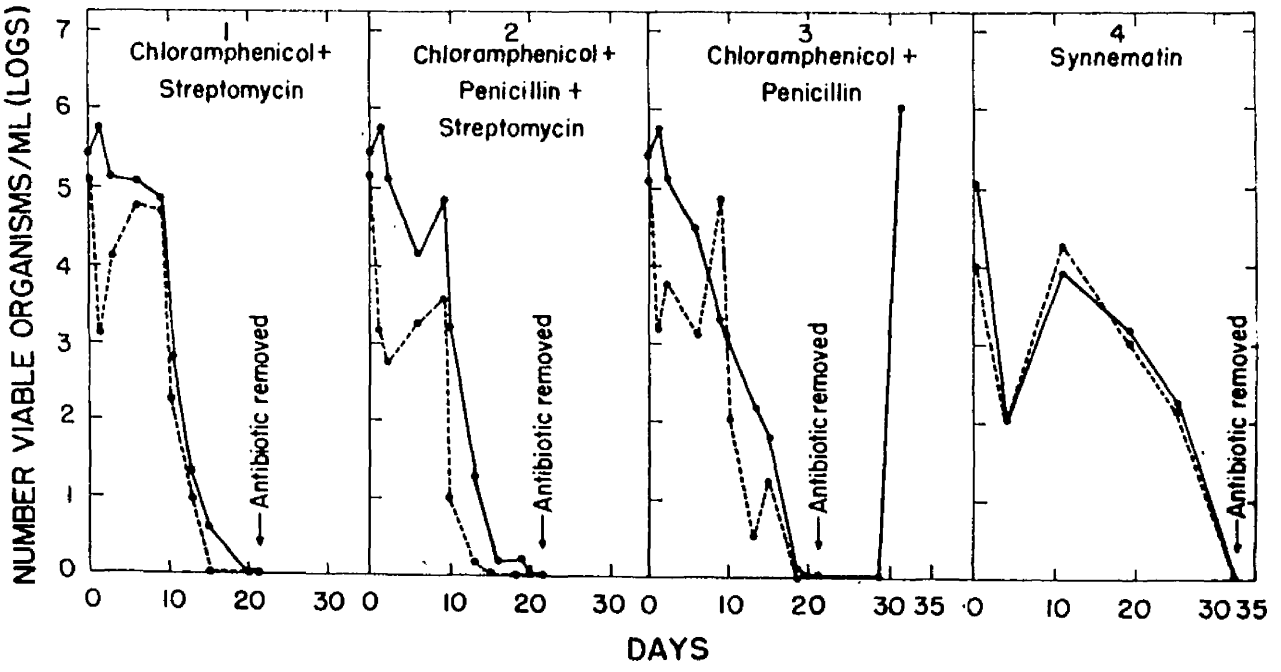


Fig. 14 - Response of S. typhi in Infected Tissue Cultures to Antibiotic Treatment.

—— = supernatant fluid.

—— = homogenized cells.

Source: Hopps et al. 1961 J. Immunol.

series of tissue culture experiments they exposed S. typhi to various antibiotics. In all 3 cultures to which chloramphenicol was added, there was an immediate fall in the culturable bacterial content of the cell-free fluid but a concomitant slight rise in the number of viable bacteria in the cells. It is feasible that the fall in bacterial content of the fluid was due in part to the direct action of the drugs and in part to an increased uptake of bacteria by the cells.

Watson believed that the intracellular position protected the bacteria from the action of chloramphenicol. However, Showacre et al.(1961) demonstrated by phase-microscopy in tissue culture cells that chloramphenicol and other antibiotics were effective against intracellular S. typhi. Intracellular bacteria were seen to undergo multiplication at intervals of about 30 minutes. When chloramphenicol, penicillin or synnematin were added to a culture, bacterial multiplication ceased simultaneously inside and outside the cell. Despite the intracellular penetration of the antibiotics, however, the number of viable bacteria in the tissue cultures did not fall markedly for the first week of exposure to antibiotics. It was this observation which led Hopps et al. to conduct the tissue culture

experiments indicated in Figure 9. It may be seen clearly from the graphs that, after an initial fall, the bacterial content of the fluid partially increased again until about the 10th day of exposure to antibiotics. Thereafter both fluid and cell bacterial counts fell at about the same rate for a further week. In all cultures which contained chloramphenicol the fluid was cleared of viable bacteria between the 14th and 18th day after exposure to the antibiotic, but the cells retained a few viable bacteria for a further few days. In the third experiment, despite 21 days of exposure to chloramphenicol and penicillin, typhoid bacilli reappeared 8 days later and eventually destroyed the tissue culture.

It is unfortunate that no information is given in this experiment about the effect on the bacilli in the cells and fluid of tissue cultures of chloramphenicol given alone. However if, as clinical evidence suggests, the rate of death of bacteria which occurs in man under the influence of chloramphenicol alone is similar to that which Hopps *et al.* found with combined therapy in tissue culture, it is clear that the withdrawal of the antibiotic before all the intracellular bacteria have been destroyed may permit a relapse to occur. In particular, if the drug is continued for less than 10 days, the number of viable bacteria

still present both intra- and extra-cellularly, is considerable, and without the presence of the bacteriostatic drug multiplication of the bacteria will be resumed and may quickly result in a relapse.

Since Chloramphenicol acts with equal speed both inside and outside the cell, it is difficult to see why at least 3 weeks of treatment are required to remove all the bacteria from the tissue culture. In an attempt to elucidate this Hopps et al. studied the effect of different antibiotics on S. typhi in the log, or rapid growth, phase and in the stationary phase. They found that with bacteriocidal drugs, such as penicillin, S. typhi in the log phase in tissue culture were killed within 48 hours, whereas at least 1 in 10 bacteria in the stationary phase survived for a week and 1 in 1000 survived for several weeks. Chloram-:phenicol and chlortetracycline showed similar effects, but were even less lethal for S. typhi. When chloramphenicol was added to tissue culture medium containing bacteria in the log phase, the total bacterial content fell much more slowly than with penicillin. When it was added to tissue culture medium containing bacteria in the stationery phase, there was a slight fall in the total viable bacterial count in the first 2 days, but

thereafter the count remained almost at the same level for 2 weeks. Hopps et al. pointed out that, although it was known already that most antibiotics were more rapidly lethal against actively growing bacteria, such prolonged survival of the stationary phase organism in a medium containing antibiotic had not previously been clearly demonstrated. They observed that, although spheroplasts, that is, round forms of bacteria, insensitive to antibiotics, were produced only extra cellularly and only by bacteriological drugs (Showacre et al, 1961) chloramphenicol might induce a prolonged resting phase analogous to the stationary phase by inducing genetic changes in the nutritional requirements of the organism.

It is known that when an actively growing bacterium is placed in a new environment in which it can survive, it enters a lag phase until it has adapted itself to the new environment. As stated earlier, Olitzki et al.(1964) demonstrated that this occurs when virulent S. typhi are ingested by phagocytes. Thus, even without chloramphenicol, there is a phase of apparent inactivity on the part of the organism. Chloramphenicol introduced at this time is relatively ineffective and there is then a period of delay, as observed by Hopps et al.,

until the bacteria adapt themselves sufficiently to approach the growing phase and then become susceptible to the action of chloramphenicol.

According to Hockster and Quastel (1963) the action of chloramphenicol on bacteria is to inhibit protein synthesis. At growth-inhibiting levels it interferes with the last stage of protein synthesis, which is the transfer of amino acids to protein. This suggests that the metabolic activities of a bacterium susceptible to chloramphenicol can continue up to the final step of protein synthesis. Such an organism is then in the lag phase of growth. The transition from the lag phase to the logarithmic growth phase is not accomplished in the presence of chloramphenicol because of the interference of the drug with the final stage of protein synthesis, without which multiplication of the organism is impossible. Death of the organism does not necessarily occur. Further, this action of chloramphenicol is completely reversible and protein synthesis resumes immediately upon removal of the drug or its reduction to a level less than that necessary to inhibit growth. If even a few of these bacteria survive until the withdrawal of chloramphenicol, they may then multiply sufficiently to cause a relapse.

It is possible that there is a further effect of

chloramphenicol. Olitzki et al.(1964) also noted that certain forms of bacteria, for example ones killed with acetone, were taken up by phagocytes but the latter were unable to digest them. It may be that exposure to chloramphenicol not only induces a prolonged lag phase but also enhances the resistance of bacteria to destruction by phagocytes. The persistence of this effect even after the withdrawal of chloramphenicol may explain the increased survival of bacteria in patients given chloramphenicol for only 1 or 2 days, and in whom the likelihood of a relapse is particularly high.

CONCLUSIONS:

The occurrence of a relapse in typhoid fever depends on the survival of sufficient numbers of bacteria for a sufficient length of time to re-invade the blood-stream late in the illness; these bacteria may survive intracellularly in untreated typhoid fever by adapting themselves to a parasitic existence in an environment where they are protected from humoral antibody. Incompetent phagocytic cells may provide a more favourable environment than others for bacterial survival.

Chloramphenicol may potentiate the occurrence of a

relapse in several ways. It depresses the production of specific antibody, partly by its bacteriostatic action and possibly also by hastening the uptake of bacteria by phagocytosis. This effect is most marked when chloramphenicol is given early in the infection. It may induce an unnatural state of "suspended animation" in some intracellular bacteria. If such bacteria are not destroyed by the cell they may revert to an active phase when the antibiotic is withdrawn and multiply to a sufficient extent to cause a relapse. It may be also that chloramphenicol renders some bacteria resistant to killing by phagocytic cells and these bacteria may then survive long after the withdrawal of chloramphenicol.

D. THE CHARACTERISTICS OF THE PATIENTS IN ABERDEEN WHO RELAPSED

Marmion's (1952) definition of a relapse was used, that is, "a return of fever of 100°F. or more, lasting 2 days or more and accompanied by any symptom attributable to typhoid fever, unless some other adequate cause can be found to account for the episode".

By this definition, there were 86 patients who relapsed,

18.3% of the 469 cases. This relapse rate agrees with the findings of Woodward et al. (1964) who stated that a total dose of 20 - 30 G. of chloramphenicol given over a period of 14 days is likely to produce a relapse rate of about 20%. Ten of these patients did not give a positive blood culture on relapse; in fact 2 patients who relapsed did not at any time give a positive isolation for S. typhi. Three women and one child relapsed twice.

The mean day of illness on relapse was 36.7 days. This was, on average, 13.0 days after the end of treatment and 22.1 days after the patient was afebrile. (These figures do not include one patient who relapsed on the 120th day of illness.)

Table 24 summarises the comparisons of patients who relapsed with other patients with regard to certain factors. It may be seen that there was no significant difference in the age and sex characteristics of the 2 groups, nor in the number of immunised individuals. The incubation periods of patients who relapsed were no different from those of other patients.

There was, however, as has been shown already, a highly significant difference in the severity of the initial

infection between the groups. Very significantly fewer patients who had a mild initial infection relapsed ($x^2 = 22.08$, $P < 0.0005$).

The duration of pyrexia on initial treatment was then compared. This comparison was restricted to patients treated with chloramphenicol, since there were not sufficient numbers of patients treated with another drug. It was found that patients who relapsed had a significantly longer mean period of pyrexia on chloramphenicol than others ($t = 2.75$, $P < 0.01$). However, when the comparison was made for the 2 separate groups "moderate" and "severe", the difference was significant only in severely ill patients ($t = 2.0$, $P < 0.05$).

The timing, dosage and duration of chloramphenicol therapy was examined for any difference between the treatment of patients who relapsed and those who did not. No significant difference was found. In patients who relapsed, chloramphenicol treatment was started at a mean of 6.8 days of illness, and was continued for 14.0 days in a mean daily dose of 29.9 mg. per Kg. body-weight. In other patients treated with chloramphenicol it was started at a mean of 7.5 days of illness, and was continued for 13.9 days in a mean daily dose of 29.0 mg. per Kg. body-weight.

TABLE 24

THE COMPARISON OF PATIENTS WHO RELAPSED WITH OTHER TYPHOID PATIENTS.

FACTOR	CASES COMPARED	SIGNIFICANT DIFFERENCE PRESENT
AGE DISTRIBUTION	ALL OTHER CASES	No
SEX DISTRIBUTION	ALL OTHER CASES	No
NUMBER IMMUNISED	OTHER CASES	No
INCUBATION PERIOD	OTHER CASES	No
SEVERITY OF INITIAL INFECTION	ALL OTHER CASES	YES
TREATMENT:		
DURATION OF PYREXIA	ALL OTHER CASES WITH CHLORAMPHENICOL	YES
DOSAGE OF CHLORAMPHENICOL	ALL OTHER CASES WITH CHLORAMPHENICOL	No
DURATION OF CHLORAMPHENICOL	ALL OTHER CASES WITH CHLORAMPHENICOL	No
DAYS OF ILLNESS BEFORE CHLORAMPHENICOL	ALL OTHER CASES WITH CHLORAMPHENICOL	No
TYPE OF INITIAL TREATMENT	ALL OTHER TREATED CASES	No
- ADULTS	- ADULTS	No
- CHILDREN	- CHILDREN	YES

When the timing of treatment was examined for severely ill patients only, it was found that these patients who relapsed again began treatment earlier than other patients, but that this difference was significant only in children ($t = 2.37$ $P < 0.05$). No comparison was possible of the type of initial treatment given to adults who relapsed but, as has been stated earlier, 19.0% of children who had chloramphenicol relapsed as opposed to none of 25 children treated initially with ampicillin.

The serum antibody levels of patients who relapsed were examined to see whether there was any clear difference between these and the antibody levels of patients who did not relapse. Unfortunately comparison of antibody levels before treatment had to be based on serum 'H' antibodies since S.typhi 'O' antibodies were estimated in only 89 patients on admission, of whom only 8 showed a positive reaction. On this basis, no difference was found in the level of serum antibodies of relapsing and other patients before treatment was started. Serum antibody levels on discharge, 'H' and 'O', were then compared, and again no significant difference was found between the two groups.

Serum antibody levels were estimated in 49 patients

on relapse. Only two patients at that time showed 'O' antibodies, but 2 other patients had S. typhi 'H' agglutination to a dilution of 1:12,800 on the first day of relapse. One patient who relapsed died. Of the remaining 85:

(i) 23 patients (27%) showed a marked rise in antibody level after relapse,

(ii) 41 patients (48%) showed no change in antibody level throughout their illness,

(iii) 21 patients (25%) showed a steady fall in antibody level after admission to hospital, despite relapse.

Once again, however, the paucity of 'O' antibodies both in patients who relapsed and in those who did not makes comparison of antibody response difficult.

CONCLUSIONS:

A study of the 86 patients in Aberdeen who relapsed showed that patients who were severely ill on admission to hospital were much more likely to relapse. Of these patients, those who took longer to respond to the initial chloramphenicol therapy were more likely to relapse than other severely ill patients. No difference was demonstrated in the schedule of chloramphenicol treatment of patients who relapsed and of other patients but, in children, none of those who were treated initially with ampicillin relapsed.

E. "POST-TREATMENT PYREXIA"

It was observed that 125 patients had a recurrence of fever during convalescence although they were completely symptom-free. For descriptive ease this phenomenon was named "post-treatment pyrexia", and it was defined as a symptomless fever, occurring during convalescence, which did not exceed a height of 100°F. but persisted for longer than 2 days, and occurred more than 4 days after the end of treatment. It was thought that this pyrexia might be the accompaniment of excretion of S. typhi during convalescence, as observed by Woodward et al. (1950) and Marmion (1952). The records of these patients were, therefore, examined and compared with those of other patients to determine any differences in this and other factors (Table 25).

The sex distribution of these and other patients was not significantly different, although there were more females than expected, but there were very significantly more children, than expected who had "post-treatment pyrexia" ($\chi^2 = 20.37$, $P < 0.0005$) there being 78 adults and 47 children.

TABLE 25

COMPARISON OF 125 PATIENTS WHO HAD "POST-TREATMENT PYREXIA" WITH OTHER TYPHOID PATIENTS

FACTOR	CASES COMPARED	SIGNIFICANT DIFFERENCE PRESENT
1. SEX DISTRIBUTION	ALL OTHER CASES	NO
2. AGE DISTRIBUTION	ALL OTHER CASES	YES
3. NUMBER WHO RELAPSED	OTHER CASES	YES
4. NUMBER OF CONVALESCENT EXCRETERS	OTHER CASES	YES
5. SEVERITY OF THE INITIAL INFECTION	OTHER CASES	YES
6. NUMBER TREATED INITIALLY WITH CHLORAMPHENICOL	ALL OTHER TREATED CASES	YES
7. CHLORAMPHENICOL THERAPY:	ALL OTHER CASES TREATED WITH CHLORAMPHENICOL	
A) DAYS OF ILLNESS BEFORE TREATMENT		NO
B) DAILY DOSE		NO
C) DURATION OF TREATMENT		NO
D) DURATION OF PYREXIA ON TREATMENT		NO
8. NUMBER OF ADULTS WHO WERE INOCULATED	ALL OTHER ADULTS	YES
COMPARISONS REPEATED FOR CHILDREN ALONE:		
1. NUMBER WHO RELAPSED	ALL OTHER CHILDREN	YES
2. NUMBER OF CONVALESCENT EXCRETERS	ALL OTHER CHILDREN	YES
3. SEVERITY OF THE INITIAL INFECTION	ALL OTHER CHILDREN	YES
4. NUMBER TREATED INITIALLY WITH CHLORAMPHENICOL	ALL OTHER TREATED CHILDREN	NO
5. CHLORAMPHENICOL THERAPY	ALL OTHER TREATED CHILDREN	NO

There was a significant deficit of patients who relapsed ($x^2 = 7.91$ $P < 0.005$) and a possibly significant excess of excreters ($x^2 = 4.99$ $P < 0.05$) in the group under consideration. Very significantly fewer of these patients than expected had a mild initial infection ($x^2 = 10.51$ $P < 0.001$). There was no significant difference between patients with "post-treatment pyrexia" and other patients in the timing, the schedule, and the effect on pyrexia of initial chloramphenicol therapy, but significantly more patients than expected who had ampicillin or "mixed" treatment initially developed "post-treatment pyrexia" ($x^2 = 8.90$ $P < 0.005$).

Because of the excess of children in this group, children and adults were next considered separately. It was found that the only significant difference between these and other adults was a deficit of inoculated patients who developed "post-treatment pyrexia" ($x^2 = 8.64$ $P < 0.005$). This difference was largely explained by the excess of women in this group.

The 47 children who had "post-treatment pyrexia", however, differed significantly from other children in several ways:

(a)/

(a) They were more severely ill on admission
($x^2 = 8.51$ $P < 0.025$)

(b) They were less likely to relapse
($x^2 = 7.96$ $P < 0.005$)

(c) They were more likely to excrete during convalescence
($x^2 = 11.58$ $P < 0.001$)

Although the children as a whole were just as severely ill on admission as children who relapsed, only 1 of the 47 relapsed after the end of the "post-treatment pyrexia". This wasnot an effect of treatment, since there was no significant difference between the number of children who had "post-treatment pyrexia" after ampicillin and after chloramphenicol. It seemed possible that in some children this pyrexia occurred instead of a relapse. In order to investigate this possibility, children with "post-treatment pyrexia" and children who relapsed were compared separately with children who had an uneventful convalescence. The following facts emerged:-

(a) that both groups were significantly more severely ill on admission than other children, but that the difference was greater in children who relapsed.

(b) that severely ill children in both groups took longer than other severely ill children to respond to chloramphenicol therapy. This difference was slightly greater in children who relapsed, but was not significant.

(c) that in severely ill children in both groups chloramphenicol therapy was initiated earlier than in other severely ill children, but that this difference was only significant in children who relapsed. (See Table 26)

TABLE 26

ALL CHILDREN WITH A SEVERE INITIAL INFECTION

TREATED WITH CHLORAMPHENICOL

	CHILDREN WHO RELAPSED	CHILDREN WHO HAD POST-TREATMENT PYREXIA	ALL OTHER CHILDREN WITH A SEVERE INITIAL INFECTION
NUMBER	9	19	10
MEAN DAY OF ILLNESS BEFORE CHLORAMPHENICOL	4.3	7.8	8.9
MEAN DAY OF PYREXIA ON CHLORAMPHENICOL	5.1	5.0	4.5
MEAN DAY OF ILLNESS	33.2	25.5	
MEAN DAY AFTER END OF CHLORAMPHENICOL	14.2	4.9	
MEAN DAY AFTER END OF PYREXIA	23.1	11.8	

From this it appeared that severely ill children with "post-treatment pyrexia" formed a group which was intermediate between severely ill children who had a normal convalescence and those who relapsed.

It has been stated that children with "post-treatment pyrexia" were more likely than other children to excrete during convalescence. However, in children who relapsed convalescence, by definition, did not begin until after recovery from relapse and, therefore, excretion which occurred in these children between the end of the initial illness and the end of relapse was ignored. When the rate of excretion <u>after the acute illness</u> was re-examined for all children, it was found that:

(a) in 47 children with an uneventful convalescence 29.7% excreted immediately after the acute illness and the incidence of excretion fell thereafter.

(b) in 46 children with "post-treatment pyrexia" 41.3% excreted immediately after the acute illness. The incidence rose to 45.7% at the time of pyrexia and fell thereafter.

(c) in 15 children who relapsed none excreted immediately after the acute illness but the incidence of excretion rose to 40% at the time of relapse and fell thereafter.

These findings suggest that the incidence of excretion

during any pyrexial typhoid infection is approximately the same, whether it be a primary infection, a relapse, or "post-treatment pyrexia". Thus, the excreter state is merely an accompaniment of pyrexia or relapse in the same way as it is found during the acute illness. It was found that "post-treatment pyrexia" occurred, on average, 5.9 days after the end of treatment, whereas relapse occurred, on average, 12.1 days after treatment was discontinued.

The writer believes that "post-treatment pyrexia" is not merely a recurrence of fever suppressed by antibiotic therapy, but the pathogenesis of this phenomenon is the same as that of relapse. Evidence has been given, when discussing relapse, to suggest that bacteraemia may occur late in convalescence. It appears that the degree of bacteraemia which is sufficient to produce "post-treatment pyrexia" occurs earlier in convalescence than the degree of bacteraemia which is capable of causing a relapse. The writer believes that during convalescence bacteria are still present in the tissues and may cause the same varying degrees of bacteraemia as occur during a primary typhoid infection. These degrees of bacteraemia during convalescence are:-

1./

1. Silent, with or without accompanying excretion. This type of primary infection will be discussed in Section V of this thesis.

2. Asymptomatic but evidenced by the presence of "post-treatment pyrexia", with or without concurrent excretion of bacteria.

3. Overt, presenting as a relapse, in varying degrees of severity.

It is possible that the higher incidence of pyrexia during convalescence in children when compared with that in adults is a reflection of the frequency with which children develop pyrexia in many infections in which adults may remain afebrile.

CONCLUSIONS:

It is suggested that the occurrence of pyrexia during convalescence, called here "post-treatment pyrexia", reflects the presence of bacteraemia to an extent which is sufficient to produce fever but not sufficient to cause a relapse. It is thought that this phenomenon is seen more frequently in children than in adults because of the greater likelihood of children in any infection to show a febrile reaction and that, the chance of post-treatment pyrexia or relapse occurring increases the earlier in the illness that the treatment is initiated.

SECTION IV

IMMUNISATION AGAINST TYPHOID FEVER

In this section an indication is given of the different methods of preparing and administering T.A.B. vaccine which have been tried since its inception. The assessment of its protective value against typhoid fever is reviewed, and the long-term effect of immunisation which was observed in patients in Aberdeen is discussed.

The phenomenon of "provocation" typhoid is briefly illustrated.

A. THE HISTORY OF ANTITYPHOID IMMUNISATION

(i) The Introduction of Immunisation

The history of anti-typhoid vaccination and its acceptance as an effective prophylactic has been fraught with argument. Claims have been made for different types of vaccines, for different dosages, and for different modes of administration; the correct answer is still in doubt.

In 1896 A.E. Wright inoculated two volunteers with a killed broth culture of typhoid organisms; in the same year, in Germany, Pfeiffer and Kolle developed a similar killed vaccine. In 1897 Wright inoculated 84 patients during an outbreak of typhoid fever in an asylum in Kent. No cases occurred amongst these individuals, as opposed to 4 amongst 114 who were not inoculated (Wright 1902). Although the outbreak was past its peak before the vaccine was given, this result encouraged Wright to proceed with vaccination of 4,000 British troops in India. Vaccination was also performed in Egypt, Cyprus, Malta and Ireland although only 4% of troops in the Boer War were vaccinated. Wright's findings, published in 1902, were, as follows:-

(a) The incidence of typhoid fever was diminished by at least one half in the inoculated.

(b) The case-mortality was diminished by at least one half in the inoculated.

(c) It is likely that the protection persists into the second and perhaps the third year after inoculation. "It is not infrequent to find an agglutinating power in the blood of inoculated persons as long as two years after the inoculation of the antityphoid vaccine".

Unfortunately there were some severe cases of typhoid fever in recently vaccinated individuals; these Wright attributed to the existence of a "negative phase" immediately following vaccination. Because of such cases, Sir David Bruce, in a report to the Advisory Board for Army Medical Services (1905) condemned the use of vaccine on board troopships and in the face of an epidemic of typhoid. He suggested inoculating half of a division at least 3 months before embarkation in an attempt to assess the protective effect of the vaccine under uniform circumstances. However, this was not feasible at that stage of the Boer War, and the Advisory Board suspended vaccination in 1903. Much bitter argument ensued, and in 1904, under Major W.B. Leishman, the first of many field studies was set up and continued for 4 years; the results, published in 1912, are summarised in Table 27. Those showed that there was a highly

TABLE 27

RESULTS OF THE BRITISH ARMY COUNCIL FIELD TRIAL OF T.A.B. VACCINE, 1904 – 1908

	NOT ATTACKED	ATTACKED	TOTAL
INOCULATED	10,322	56	10,378
NOT INOCULATED	8,664	272	8,936
TOTAL:	18,986	328	19,314

$\chi^2 = 180$ $P < 0.0001$.

SOURCE: REPORT OF THE ANTITYPHOID COMMITTEE 1912.

significant reduction in the incidence of typhoid fever amongst inoculated personnel during this time. Leishman advocated two doses of 750 - 1,000 million bacteria and a reduction of the lethal temperature in preparation of the vaccine to 53°C. (Report of the Antityphoid Committee, 1912). On this basis, vaccination was accepted by the British Army and has remained in use since, despite many doubts and setbacks.

(ii) Preparation of Vaccine

Wright's original vaccine was a broth suspension of typhoid organisms killed by heating to 63°C. and preserved in 0.5% phenol. Numerous methods of killing bacteria have since been used; for example, different degrees of heat, ether, alcohol, phenol and iodine (Gay 1918). Heating to 53°C. has long been the most widely accepted, but two other methods have been advocated by some workers:

Firstly, since Vi antigen is sensitive to heat and carbolic, alcohol was used both to prepare and to preserve the new Vi-containing vaccine which Felix produced in 1941.

Secondly, acetone was used by Landy (1953) also in order to retain Vi antigen in vaccine. This followed the observation by Henderson (1939) that acetone acts like alcohol on Vi antigen to stabilise it.

The relative merits of these two preparations will be considered in detail later in this section.

As well as killed cultures, living cultures were used by several workers (Castellani 1909) but were generally thought to be too dangerous for use in man. Bacterial extracts were tried and found wanting, as were sensitised cultures. The latter are cultures first heated with an immune serum and then killed; this method was first used by Besredka (1902) who devoted many years to its study and development. He and Metchnikoff carried out extensive studies on chimpanzees and produced experimental proof of immunity in these animals (Metchnikoff & Besredka 1911), and although their vaccine is no longer used, their contribution to our knowledge of local and general immunity was immense.

(iii) Preservation of Vaccine

Until the discovery of the Vi antigen, phenol was the usual preservative for vaccine, although formalin had been tried (Grasset and Gory 1927). When Felix introduced his new vaccine in 1941 he used alcohol to preserve as well as to prepare it. Landy's acetone-prepared vaccine was preserved by drying, and freeze-drying has since been used to maintain the stability of heat-phenolised vaccine also.

(iv) Strains of Typhoid Bacillus used in Vaccine

Wright's original strain "G" was replaced before the first World War by a more easily emulsified one of low virulence, called the "R" or Rawlings strain after the patient from whom it was isolated. This strain continued to be used for more than 20 years. Then it was realised that a "smooth" strain was more virulent than a "rough" one and also gave a better vaccine (Arkwright 1921 and 1927). In 1933 Perry, Findlay and Bensted noted that the Rawlings strain being used was rough and of low virulence. Bensted discovered by accident (1958) that mouse-passage gave a smooth strain five times more virulent than the original strain. By this method, that is, by injecting this strain into mice and allowing it to multiply before re-isolation, Perry, Findlay and Bensted (1933) produced a "rejuvenated" Rawlings strain, called Raw-Ben after Bensted. In Britain this strain was used alone in the preparation of vaccine until 1945, then in combination with a freshly isolated smooth virulent strain Ty.2 for two years more until it was discarded completely. Ty.2 was first isolated in 1918 during an outbreak of typhoid fever in Russia (Weil and Felix 1920). In an attempt to give protection against a wider range of strains of S. typhi, two "wild" strains were added to Ty.2 in 1955 and this combination is still in use. The strains used

TABLE 28

THE TYPHOID STRAINS USED IN THE BRITISH ARMY VACCINES, 1933-1960

DATE	STRAINS		TREATMENT
UP TO 1933	RAWLINGS	100%	PHENOLISED
1933 TO NOVEMBER, 1943	RAW-BEN	100%	PHENOLISED
NOV. 1943 TO NOV. 1945	RAW-BEN	100%	ALCOHOLISED
NOV. 1945 TO JULY 1946	RAW-BEN T.240	50% 50%	ALCOHOLISED
JULY 1946 TO MAY 1947	RAW-BEN T.272	50% 50%	ALCOHOLISED
JUNE 1947 TO JULY 1947	RAW-BEN TY 2	50% 50%	ALCOHOLISED
JULY 1947 TO AUG. 1949	TY 2	100%	ALCOHOLISED
AUG. 1949 TO JULY 1954	TY 2	100%	A. ALCOHOLISED B. ALCOHOLISED
JAN. 1955 TO APRIL 1959	TY 2 T 15 T 18	33.3% 33.3% 33.3%	PHENOLISED PLUS TETANUS TOXOID 10 LF (T.A.B.T.)
FEBRUARY 1959	TY 2 T 15 T 18	33.3% 33.3% 33.3%	PHENOLISED PLUS "MUELLER" TETANUS TOXOID, 20 LF (T.A.B.T. INTRADERMAL).

SOURCE: SAYERS, M.H.P. "RECENT DEVELOPMENTS IN ANTI-ENTERIC VACCINE IN THE BRITISH ARMY" - THESIS FOR THE DEGREE OF DOCTOR OF MEDICINE, LONDON UNIVERSITY, 1961.

in the British Army at different times are summarised in Table 28. In America the Raw-Ben strain was replaced by a smooth virulent strain called Panama 58 (Sayers 1961).

(v) Method of Administration

There are five possible routes of administration of vaccine: intravenous, intramuscular, subcutaneous, intradermal and oral. Wright's original route was subcutaneous, but in view of the extent of the reaction in the form of local inflammation and systemic fever and shock which sometimes resulted, he attempted immunisation by the oral route. He found, however, that in previously immunised individuals there was little or no response to oral vaccine and what did develop was of short duration (Wright 1904). This method was investigated further by Besredka (1927) who insisted that vaccine given orally was as effective as by injection, provided that the host was sensitised beforehand by the administration of ox-bile. He said that ox-bile altered the protective intestinal mucosa to allow direct contact between the bacteria and the "receptor" cells of the host, and claimed that oral vaccine was "innocuous, effective and rapid in action". From time to time oral vaccination has again been advocated because of the undoubted absence of upset to

the host, but it is generally agreed that it does not give as good protection as vaccine given by subcutaneous injection. Recently, however, a series of tests on 30 pre-school children in Rumania (Vladoianu et al. 1965) has indicated that there may be a place for oral vaccination. The children were given a massive dose of bacterial vaccine on each of 3 consecutive mornings and satisfactory levels of serum antibodies were produced. A second similar course was given one month later. Chick-embryo tests showed that the second course of vaccine had no effect on the level of antibodies produced after the first oral course. The absence of effect was attributed by Vladoianu and his colleagues to a local barrier created in the intestinal lymphatics by primary vaccination, that is, an artificial blockade similar to the natural blockade propounded by Hädson (see pages 38-40). They suggest that, on this basis, it would seem reasonable to give a first course of oral vaccine to produce quick local immunity followed by parenteral vaccine 4 weeks later to boost general immunity, and that this method would be of particular value in young children or sensitive subjects. It is known that antibody is produced by plasma cells in intestinal lymphoid tissue (Coons et al. 1956) and it is possible that this does create a local barrier. This would indeed appear justifiable in the face of an

epidemic, but it would be of interest, before using this method generally, to know how long the failure of antibody stimulation by repeated oral vaccine persists, that is, how long the hypothetical local barrier remains.

It would be of value to compare, by field trial, the effects of this combined method of immunisation with those of single and multiple dose parenteral immunisation alone.

Intravenous administration was tried by a few workers (Nicholle et al. 1912) but it was found to cause a severe and often dangerous systemic reaction and it was not generally adopted. Its marked pyrogenic effect has caused it to be used in chronic diseases, such as rheumatoid arthritis, to stimulate non-specific defence mechanisms, but it is not thought to be of great value (Parish and Cannon 1962).

Intramuscular injection usually occurs only by accident when subcutaneous injection is intended; it is of no more value than subcutaneous injection and may cause severe systemic reaction. (Gay 1918).

Intradermal injections of vaccine were first used extensively by Tuft and Tuft, Yagle and Rogers in 1931. They compared the five possible routes of administration and stated that

the intradermal route in man gave a slightly higher, although slower, response which was maintained for longer. They gave 4 intradermal injections of 0.05 ml., 0.1 ml., 0.15 ml. and 0.2 ml. at weekly intervals, as opposed to 4 doses of 0.5 ml. at weekly intervals subcutaneously, since they considered that 0.2 ml. was the maximum volume of fluid tolerable intradermally. They found that systemic reaction to vaccine by this route was only slight. This, and the good antibody response which resulted, were attributed by them to the slower absorption from the intradermal site or to the abundance of reticulo-endothelial cells in the skin. They also pointed out that this method was very economic of vaccine.

Perry (1937) confirmed these findings; but Siler and Dunham (1939) believed that whilst the intradermal route was adequate for "booster" doses of vaccine, it did not give as much protection as the subcutaneous route when used for primary inoculation.

In 1940 Tuft stated that 3 doses of intradermal vaccine were sufficient, that is 0.1 ml., 0.15 ml., and 0.2 ml. at weekly intervals. He supported this statement by showing that the serum thus produced gave better protection in mice than did immune serum

obtained after subcutaneous inoculation. However, Luippold (1944) asserted that the intradermal route gave both lower levels of serum agglutinins and poorer mouse protection, although he admitted that there was less systemic upset after intradermal injection and that it was economic of vaccine. Because of Luippold's findings the intradermal route was not adopted in America.

About this time alcoholised vaccine was introduced in Britain by Felix (1941). Since alcohol given intradermally causes sloughing, this route was not investigated again until phenolised vaccine was re-introduced in the British Army in 1954. Between then and 1958 a comparison was made of scratch, multi-puncture and intradermal routes of administration (Sayers 1961). Only the intradermal method yielded consistently good results in human volunteers. At the same time an extensive comparison of intradermal and subcutaneous immunisation was carried out on the basis of mouse protection tests. These results showed that intradermal vaccine gave a response equal to if not better than subcutaneous (Barr et al. 1959). On the basis of these results the intradermal route for primary vaccination was finally adopted by the British Army in April, 1958.

(vi) Strength of Vaccine

At the beginning of the First World War monovalent vaccine containing 1000 million bacteria per ml. was in use. In 1915 triple vaccine containing also 750 million bacteria per ml. of both S. paratyphi A and B was introduced in the British Army. The quantity of the last two components was reduced to 500 million organisms per ml. in 1949

(vii) Dosage of Vaccine

The number of injections given for primary vaccination, and the volume of each, has varied only slightly throughout the years. Wright originally gave only one injection, but he found much less systemic reaction when the same dose of vaccine was given in two injections separated by several days. The first injection contained 750 - 1000 million bacilli, and the second 1,500 to 2,000 million. When paratyphoid vaccines A and B were added, the dosage of S. typhi was changed to 750 followed by 1,000 million organisms, that is, 0.5 followed by 1 ml. During the First World War a booster dose was given 2 years later. This routine was generally followed until the early days of intradermal vaccine when it was felt that more injections were required to compensate for the smaller volume of each. However, it was soon found that 2 doses were as effective as 3 or 4.

The interval between doses has varied rather more. During the First World War the interval was 8 - 10 days, and at the beginning of the Second World War it was 10 - 14 days. However, it was observed by Glenny (1925) that about 10 - 14 days usually elapsed from the time of a first injection of vaccine before the level of serum antibodies reached its maximum, and that an injection given after that interval produced a higher and more prolonged response. With the addition of tetanus toxoid to T.A.B. vaccine, the interval between doses had to be increased to 4 - 6 weeks to obtain maximum immunity to tetanus. However, Schutze (1941) compared the serum "O" antibody levels produced in two groups of mice, in whom two injections of vaccine were given at intervals of 1 week and 4 weeks. He found that the antibody response in the second group was 50% higher than when the interval between the doses was only 1 week. In 1946 the British Army increased the interval to 21 - 28 days and also gave an immediate "booster" dose to all troops on their arrival in an area where typhoid was endemic (Sayers 1961). This regime is still in force.

The types of T.A.B. vaccine at present available in Britain are:-

1./

1. Heat-killed phenol-preserved T.A.B. Vaccine, given in two doses of 0.5 ml. with an interval of 7 - 28 days. A third dose of 1 ml. may be given after about six months. This vaccine contains per ml. 1,000 million S. typhi, and 500 or 750 million each of S. paratyphi A and B. S. paratyphi C may also be added in the same quantity. (This vaccine is also available combined with tetanus toxoid or with cholera vaccine.)

2. "T.A.B. Intradermal" vaccine, which contains twice as many organisms per ml. as the above. This vaccine should not be given intramuscularly since over dosage may cause local skin necrosis. All doses are 0.1 ml. given intradermally.

3. Alcohol-treated enteric vaccine, which is very rarely used since it cannot be combined with tetanus toxoid and cannot be given intradermally.

(viii) Assessment of the Protective Value of T.A.B. Vaccine

The chief use of T.A.B. Vaccine is for mass immunisation in an attempt to prevent the spread of typhoid fever in a crowded community. Until recently most of the information about its effect has, therefore, come from both World Wars, when it has

been possible to record and sometimes to test its effect in just such a population.

It is undoubtedly true that the vaccine used during the First World War reduced the incidence of enteric fever. Even if one accepts a lowered overall incidence due to improved standards of hygiene, this is hardly sufficient to account for a reduction in morbidity of approximately (48) times from that in the Boer War (Table 29).

By modern standards, however, the British Army Council trials in 1904-08, by which the use of vaccine was vindicated, were very badly conducted. The vaccine was often resterilised and thus varied in quality; varying doses were given; the distinction between typhoid and paratyphoid fever was often not clear, and the diagnosis was often based only on serology. Moreover, the two groups were differentiated by whether they volunteered for immunisation or not, a factor which would immediately invalidate any modern trial. Many men were immunised during or after an outbreak and, finally, the observers were biased in favour of immunisation (Cockburn 1955). However, at the beginning of the Second World War these criticisms had not yet been published, and the use of T.A.B. vaccine was almost universal.

TABLE 29

COMPARISON OF THE INCIDENCE OF ENTERIC FEVER IN THE BOER WAR AND IN THE FIRST WORLD WAR

	ANNUAL INCIDENCE	ANNUAL DEATH RATE	TOTAL CASES	TOTAL DEATHS	MEAN STRENGTH
BOER WAR	105.0	14.6	57,684	8,022	208,226
1914-18 WAR	2.35	0.139	20,139	1,191	APPROX. 2 MILLION

SOURCE: THE HISTORY OF THE GREAT WAR, MEDICAL SERVICES, PATHOLOGY, (1923) P.211.

Doubt was first cast on the experimental assessment of the immunising power of T.A.B. vaccine by Felix (1924), who showed that whereas immunity was measured by the level of 'H' antibodies produced in serum, it was in fact 'O' antibodies which were responsible for immunity. Felix's discovery of 'Vi' antigen, however, led him to think that, although both 'O' and 'Vi' antigens effected virulence, 'Vi' was mainly responsible for the production of immunity and that, therefore, a vaccine which contained large amounts of Vi antigen would be more effective than one which contained little or none (Felix & Pitt 1951). When he wrote about his new alcohol-killed and preserved vaccine in 1941 he stated that on subcutaneous injection it stimulated the formation of protective 'Vi' antibody in nearly 50% of men and also that it produced less systemic reaction (Felix 1941, Felix, Rainsford and Stokes 1941). In 1943 this vaccine was introduced in the British Army in all zones except India and South-East Asia. Unfortunately it did not have the expected effect of reducing the incidence of typhoid fever. On the contrary, there were a number of severe outbreaks in the next 10 years which led to much doubt as to the efficacy not only of alcoholised vaccine but of immunisation in general.

One of the first comparative observations on different types of vaccine was made by Boyd (1943 a.b.) who noted that when British Army T.A.D. vaccine was introduced into an Italian prisoner-of-war camp the incidence of typhoid fever fell remarkably and also that British troops as prisoners of war enjoyed an immunity in insanitary conditions where other prisoners did not. He attributed these findings to the fact that British vaccine was prepared from a virulent, Vi-containing strain of S. typhi, whereas the Italian vaccine was prepared from a strain of low virulence, and he substantiated this belief with mouse-protection tests. It is advisable to note here that the British vaccine to which he referred was heat-:phenolised, and not alcoholised as stated by some writers (Spaun 1957, Huckstep 1962). At the same time Boyd noted that the formalised toxoid used by Grasset in South African troops appeared to give protection equal to that of the British vaccine.

The first of several notable outbreaks of typhoid fever amongst immunised individuals occurred in 1944, when 79 out of 230 at risk, that is 34%, developed typhoid fever in a British unit in Germany (Jordan and Jones, 1945). Almost all the men had been immunised in the previous 12 months, most with phenolised vaccine. Jordan and Jones stated that although

some were protected from attack, the course of the illness was not modified by immunisation.

In the following year there was an outbreak of typhoid fever in Egypt in a British R.A.F. unit at Shallufa. All personnel had been immunised, most of them within the previous year, and some with alcoholised vaccine. Of 747 men at risk, 110 (15%) developed typhoid fever (Anderson and Richards 1948). The illness was severe and there was a mortality rate of 10% which led the authors to the same conclusion as Jordan and Jones, namely that T.A.B. did not modify the course of the illness.

In 1948 in Palestine a further outbreak created serious doubts as to the efficacy of vaccine in general and of alcoholised vaccine in particular. Both typhoid and paratyphoid fevers occurred simultaneously in a British unit, and 61% of troops developed one or other or both infections. Most of the 65 soldiers involved had recently received alcoholised vaccine, and some had also had phenolised vaccine.

Finally, in Abyad, Egypt, in 1950 there were two successive outbreaks which showed that not only did immunisation not necessarily give protection but that neither did a previous

attack of typhoid fever (Marmion et al. 1953). In April, 1950, there was an outbreak caused by S. typhi 'phage type 'J' which affected 84 of 657 persons at risk, an attack rate of 13%. Three months later a second outbreak occurred, caused by S. typhi 'phage type 'E'. Of 688 individuals at risk, 235 (34%) developed typhoid fever, 11 of whom had also been infected in April. Most personnel had recently received alcoholised vaccine from a single batch. These two outbreaks demonstrated clearly that the effect of different typhoid vaccines could not be based on the comparison of different outbreaks, since the attack rates in the same circumstances were obviously affected by the difference in the causative organism.

Whether or not it was coincidental, it thus appeared that the increased incidence of typhoid fever had begun after the introduction of alcoholised vaccine in 1943. In India also, where phenolised vaccine had continued to be used, the incidence of typhoid was low (Ahuja 1957). This may in part have been due to the fact that the dose of alcoholised vaccine, because of the possible adverse effect of 1 ml. of 25% alcohol given subcutaneously, was half that of phenolised vaccine.

By 1948 it was obvious that the protection tests in mice and the Vi antibody estimations in humans performed by

Felix and his co-workers (Felix 1941, Felix et al. 1941, Climie 1942) which indicated that alcoholised vaccine should give good protection, were not being borne out in human infection. Drysdale (1947) compared vaccines made by the two different methods from the same strain at the same time, and found only quantitatively better Vi antibody production with alcoholised vaccine. He also performed simultaneous mouse protection tests and could show no difference between the vaccines. The results of the major laboratory findings on antibody production after vaccination were ably surveyed by Spaun (1957) who concluded that "vaccine prepared from culture killed by alcohol, or by another organic anhydrous solvent, as a rule causes more pronounced 'Vi' antibody production than the conventional heat-killed vaccine. The 'O' antibody production is practically the same after vaccination with either vaccine. Finally, the 'H' antibody production is the least with alcoholised vaccine."

Spaun pointed out that the results of mouse protection tests did not always agree with the agglutination titres. He also observed that, since these mouse protection tests "express the sum of the actions of 'O' and 'Vi' antibodies, and the results, besides, depend on the size of the challenge dose", the value of the tests was, at best, doubtful.

The same conclusion had been reached by British Army officials in 1948, and it was obvious that a field trial to compare the protective effect of alcoholised and phenolised vaccines in man would be of immense value. Accordingly, one such trial was initiated in 1949 and ran for 5 years. Servicemen with an odd unit number were given alcoholised vaccine, and those with an even number were given phenolised. The dose of alcoholised vaccine was double that given previously, so that both vaccines were given as 0.5 ml. followed by 1 ml. 3 - 4 weeks later. Unfortunately the overall incidence of typhoid fever fell markedly soon after the beginning of the trial, and the number of cases which occurred was insufficient to allow definite conclusions to be drawn (Sayers 1961).

When it became obvious that the Army trial was going to be a failure, the World Health Organization decided to sponsor a series of field trials in order to determine:-

(a) whether immunisation with any vaccine is of value in the prevention of typhoid fever,

(b) if so, whether one vaccine affords better protection than another,

(c) whether there is any correlation between laboratory potency tests and the effect in man.

The first trials were conducted in Yugoslavia between 1954 and 1960 (Yugoslavia Typhoid Commission 1962). Some 36,000 volunteers were allocated by a strictly random method to one of three groups: one given alcoholised typhoid vaccine, one given phenolised vaccine, and a control group which was given phenolised Shigella flexneri vaccine. Participants were given two subcutaneous injections of between 15 and 30, and 75 and 150 million bacteria, depending on age, at an interval of 3 weeks. A booster dose was given 1 year later. Only a diagnosis based on positive blood culture was taken as proof of typhoid fever.

Between 1954 and 1960 there were 15 cases of typhoid fever diagnosed in the phenolised vaccine group, 32 in the alcoholised vaccine group, and 55 in the control group. There was, therefore, demonstrated a significant protective effect of phenolised vaccine (about 70% protection rate), but alcoholised vaccine was not shown to be of significant value.

Concurrent serological tests showed that alcoholised vaccine stimulated the production of greater amounts of 'Vi' antibody, a result which did not correspond with its poorer protective power in the field. Active mouse-protection tests,

on the other hand, showed that phenolised vaccine was significantly better than alcoholised, which suggested that this test might reflect the effect of vaccine in man.

Although these trials showed that heat-phenolised vaccine was effective for at least 3 years, the liquid preparation used was unstable and laboratory potency tests were inconclusive. Landy (1953) had shown that acetone-dried vaccine was very stable, and Edsall et al. (1960) had shown it to be effective in protection tests in chimpanzees. It was decided to conduct two further trials to compare the effectiveness of a stable, dried, heat-phenolised vaccine with that of an acetone-killed and freeze-dried vaccine. Both vaccines were prepared at the Walter Reed Army Institute of Research, and the trials were conducted in Yugoslavia and in British Guiana on the same basis as the previous ones in Yugoslavia.

The trial in Yugoslavia (Yugoslavia Typhoid Commission 1964) showed that acetone-dried vaccine had a significant effect in both children and adults (79% protection rate) but that heat-phenolised vaccine gave significant protection only to those under 15 years of age (average protection rate 51%). The figures are shown in Table 30.

TABLE 30

RESULTS OF FIELD TRIALS OF HEAT-PHENOLISED AND ACETONE-DRIED VACCINES

TYPE OF VACCINE	CASES PER 1,000		
	YUGOSLAVIA (2 DOSES)	BRITISH GUIANA	
		1 DOSE	2 DOSES
ACETONE-DRIED	3.2	0.0	0.2
HEAT-PHENOL	7.3	0.9	1.1
CONTROL (TETANUSTOXOID)	14.9	4.0	4.1

SOURCES: YUGOSLAV TYPHOID COMMISSION (1964)
TYPHOID PANEL, U.K. DEPARTMENT OF TECHNICAL CO-OPERATION, (1964)

The trial in British Guiana (Typhoid Panel, U.K. Dept. of Technical Co-operation 1964) which was conducted on school children only, confirmed the finding that acetone-dried vaccine gave significantly better protection than phenolised but that both gave a significant degree of protection to children (94% and 71% respectively). The reason for the poorer protection afforded to adults in Yugoslavia by phenolised vaccine is not known. It was observed in British Guiana that this vaccine tended to decrease in effect as the time from vaccination increased: this did not occur with acetone-dried vaccine.

It may also be seen from Table 30 that children in British Guiana who were given only 1 dose of vaccine initially were afforded up to 2 years from the date of injection, at least as good protection as those who received 2 injections 1 month apart. The Typhoid Panel commented that "further studies in non-endemic areas would be required before a confident answer on the value of one dose of vaccine could be given". This finding does, however, support that of the previous trials in Yugoslavia that, 4 years after initial injections, there was no obvious difference in the protection received by those who had a third dose one year later and those who did not.

Concurrent laboratory assays showed no difference in 'Vi' antibody levels produced by each vaccine to correspond with the difference in protective effect (Benenson 1964). 'O' antibodies gave inconsistent results: in the 1954-60 studies 'O' agglutination was better in those who were given the more effective (phenolised) vaccine, whereas in the 1960-62 studies the opposite occurred. Surprisingly, the 'H' antibody, which has never been shown to affect resistance to typhoid infection (Tully et al. 1963) was the only factor in this study which could be correlated with the degree of protection afforded by vaccination. The phenolised vaccine in the earlier trials gave high levels of 'H' agglutination, but the acetone-dried vaccine gave even better levels.

Further trials conducted in the U.S.S.R. between 1958 and 1962 compared heat-killed, alcoholised, and chemical vaccine (that is, one which contains only antigens and no bacterial cells) and showed that the heat-killed vaccine was the most effective. (HEJFEC 196
They also indicated, however, that the size of the dose of alcoholised vaccine was important, a dose of 600-1,000 million organisms being effective where one of 200-300 million did not appear to be. Since the dose of alcoholised vaccine used in the first field trials in Yugoslavia was a maximum of 150 million

organisms, it is possible that a higher dose of bacteria would have shown a result more favourable to alcoholised vaccine.

In previously mentioned trials it was shown that individuals who failed to receive a second or booster dose of vaccine appeared to show equally good protection. These people were generally different from those who had a complete course of injections in that the omission was due to reluctance to co-operate further. However, in one of the field trials in the U.S.S.R., conducted on a random basis, it was found that there was no difference in the protection conferred by a single dose of chemical vaccine from that given by two doses at an interval of 20 - 30 days.

The conclusions drawn from all these trials were summarised by Cvjetanovic and Uemura of the World Health Organization (1965). These conclusions are:-

(a) That acetone-dried and heat-phenolised vaccines are both effective in man, and that acetone-dried vaccine is superior.

(b) That the effect of phenolised vaccine declines more rapidly than that of acetone-dried, but that both are potent for longer than was previously supposed (See Figure 15). As long as 3-5 years may elapse before a booster dose is required with these vaccines.

EFFECTIVENESS OF ACETONE DRIED AND HEAT PHENOLISED VACCINES AS OBSERVED IN CONTROLLED FIELD TRIALS IN BRITISH GUIANA, POLAND, USSR, AND YUGOSLAVIA.

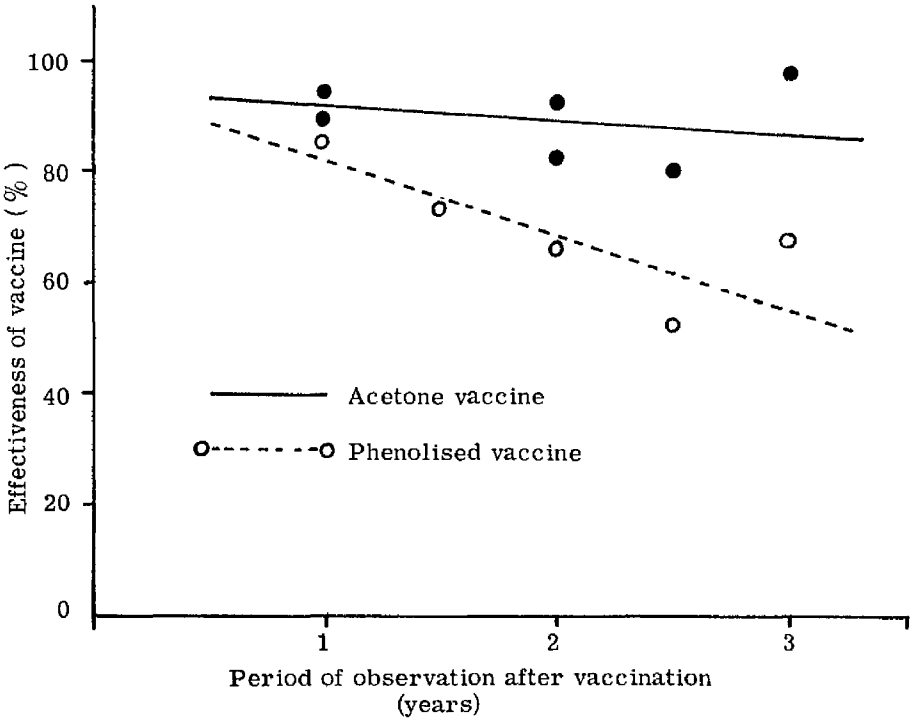


Fig. 15 - The Effectiveness of Acetone-dried and Heat-phenolised Vaccines as observed in Controlled Field Trials in British Guiana, Poland, U.S.S.R. and Yugoslavia

Source: Cvej, Ienovic and Umeura B. W.H.O. 1965.

(c) That alcoholised vaccine is less effective than either of these.

(d) That some vaccines may give protection with only one dose.

(e) That active mouse protection tests seem to be the best method at present available for measuring the potency of typhoid vaccines, with the exception of alcoholised vaccine, but that these tests are subject to wide variations.

(f) That serological tests suggest that the level of 'H' antibodies is the most reliable index of the effectiveness of typhoid vaccines.

It is clear from these conclusions that, whilst the effectiveness of certain vaccines in protecting man from typhoid fever has undoubtedly been established, further investigations are necessary before the exact nature of the protective agent, in animals or in man, is completely understood.

B. THE EFFECTS OF PREVIOUS ANTITYPHOID IMMUNISATION IN ABERDEEN

The Aberdeen outbreak occurred in an area where typhoid fever was not endemic and where there was no antityphoid inoculation programme. The population at risk was similar to that of other areas of Great Britain and there was no reason to suppose that the incidence of immunised individuals was unusual. It was felt that an analysis of the long-term effect of T.A.B. vaccine on patients in this outbreak might be of value.

Source of data

The data for this analysis was obtained partly from the patients and partly from the Ministry of Defence. All patients were questioned about the dates and number of injections which they had received in the past from any source, and all ex-Service-:men provided their Service number. These numbers were then correlated with the information kindly provided by Major-General M.H.P. Sayers, Ministry of Defence, about the types of vaccine

used at different times by the British Army (Table 28). Information was also obtained about the vaccines used in the Royal Navy and Royal Air Force since the beginning of this century.

Unfortunately, it was not possible to assess an attack-rate since the total number of persons at risk was not known. Of 10,671 contacts who were examined, only 1 in 10 was known to have been immunised, as opposed to 1 in 5 of the typhoid patients, but information about the immunisation state of the contacts was by no means complete.

The Characteristics of the Immunised Patients

There were 87 of the 469 cases of typhoid fever who had previously been immunised (see Table 31), and a further 4 patients who were immunised in May, 1964, during their incubation period. These 4 patients were not included in the subsequent analysis, but will be discussed later.

Since it is generally believed that the effect of immunisation lasts for approximately 3 years, all calculations were repeated excluding those patients immunised after 1960. However, no difference was found in any of the results.

TABLE 31

DISTRIBUTION OF THE TYPES OF VACCINE RECEIVED BY INOCULATED ADULTS, SHOWING DATES OF LAST INJECTION

CORRESPONDING AGE GROUPS ARE SHOWN IN BRACKETS.

DATE:	1950-63	1940-49		1910-39	1910-63
AGE GROUP(YRS)	(15-29)	(30-44)	(45-59)	(60 +)	ALL AGES
TYPE OF VACCINE					
PHENOLISED	14	16	17	18	65
ALCOHOLISED	2	11	1	1	15
PHENOLISED AND ALCOHOLISED	0	4	2	0	6
ALL INOCULATED ADULTS:	16	31	20	19	86

The comparison of inoculated with uninoculated patients is shown in Table 32.

There were many more inoculated men than women, as might be expected since the majority had been immunised in the Armed Forces: 40% of men were immunised, but only 5% of women. Only one child had been immunised, and so comparisons were based only on adults. There were significantly more inoculated than uninoculated men in the 30-44 year-old age group and fewer in the 15-29 year age group ($\chi^2 = 19.64$ $P < 0.005$). Once again this was explained by the proportion of each group who were required to do National Service.

There was no significant difference in the incidence of relapse between inoculated and uninoculated adults, but there were significantly fewer inoculated adults who excreted S. typhi during convalescence ($\chi^2 = 9.98$ $P < 0.0050$). This agrees with the observations of Fletcher (1918) who investigated 1,000 men who were convalescent from typhoid fever and found that prophylactic inoculation diminished the frequency of the carrier state but did not abolish it.

It is possible that immunisation reduces the likelihood

TABLE 32

COMPARISON OF INOCULATED AND UNINOCULATED PATIENTS

FACTOR	CASES COMPARED	SIGNIFICANT DIFFERENCE PRESENT
1. SEX DISTRIBUTION	ALL	YES
2. AGE DISTRIBUTION	ALL	YES
3. NUMBER WHO RELAPSED	UNINOCULATED	NO
4. NUMBER OF CONVALESCENT EXCRETERS	UNINOCULATED	YES
5. DISTRIBUTION OF THE SEVERITY OF THE ILLNESS	ADULTS	YES
6. FURTHER COMPARISONS ON THE BASIS OF SEVERITY OF THE ILLNESS:		
A) NUMBER OF INJECTIONS OF VACCINE	WITHIN THE GROUP OF INOCULATED	NO
B) TIMING OF LAST INJECTION OF VACCINE	WITHIN THE GROUP OF INOCULATED	NO
C) TYPE OF VACCINE	ADULTS	NO
7. DISTRIBUTION OF THE SEVERITY OF THE ILLNESS IN AGE GROUPS		
A) ALL INOCULATED ADULTS: 15-29 YRS.	ALL	YES
B 30-44 YRS.	UNINOCULATED	NO
45-59 YRS.	ADULTS IN	NO
60+ YRS.	SAME AGE GROUP	YES
B) ALL ADULTS INOCULATED WITH PHENOLISED VACCINE: 15-29 YRS.	ALL	YES
30-44 YRS.	UNINOCULATED	NO
45-59 YRS.	ADULTS IN	NO
60+ YRS.	SAME AGE GROUP	YES
C) ALL ADULTS INOCULATED WITH ALCOHOLISED VACCINE: 30-44 YRS.	ALL UNINOCULATED ADULTS IN	NO
45-59 YRS.	SAME AGE GROUP	NO
8. MAXIMUM HEIGHT OF 'H' AGGLUTINATION		
A) ALL INOCULATED ADULTS	ALL UNINOCULATED ADULTS.	NO
B) TYPE OF VACCINE	WITHIN THE GROUP OF INOCULATED ADULTS	NO
C) NUMBER OF INJECTIONS OF VACCINE	WITHIN THE GROUP OF INOCULATED ADULTS	NO
D) TIMING OF LAST INJECTION OF VACCINE	WITHIN THE GROUP OF INOCULATED ADULTS	NO
E) DISTRIBUTION OF THE SEVERITY OF THE ILLNESS.	WITHIN THE GROUP OF INOCULATED ADULTS	NO

of isolation of bacteria at all stages of the illness, since it has been shown in Section II (Appendix 1.A) that there were very significantly more immunised individuals in whom the diagnosis was only clinically confirmed than there were confirmed bacteriologically ($x^2 = 25.72$ $P < 0.0005$).

It has been stated previously that very significantly more adults who were immunised had a mild illness than adults who were not ($x^2 = 31.59$ $P < 0.0005$). When this difference was examined in age groups it was found to be significant only for patients aged 15 - 29 and 60 years and over, being more marked in the latter group. (15 - 29 years $P < 0.005$, 60 years and over $P < 0.001$).

[It may be remarked that this age difference does not correspond with the age difference quoted in Section II where the severity of the illness is discussed. It was observed there that the sex-difference, which was believed to be due to the distribution of immunised individuals, occurred in the 45-59 year age-group, but not in the 15-29 year age-group. This apparent disparity is explained by the fact that the large number of uninoculated females in these two groups affected the significance of the calculations.]

There was no significant difference in the severity of the illness between different age-groups in uninoculated patients

and it was considered possible that this age difference was a reflection of the variation in the immunisation history of the patients in the different age-groups. Comparisons of these histories were, therefore, made within the group of inoculated patients on the basis of the severity of the illness.

No difference in effect on "severity" could be demonstrated by comparison of patients who had 1, 2 and 3 or more previous injections of vaccine. When the dates of the last injection received by each individual were compared, no difference in effect was found. It was observed, however, that the "time" groups 1910-39, 1940-49 and 1950-63 contained the same individuals as the age-groups 60+, 30-59 and 15-29 respect-:ively. These time groups corresponded approximately with the periods "First World War and after", "Second World War" and "after Second World War".

The type of vaccine given to each individual was then examined. The majority of patients had received phenolised vaccine, but during the Second World War and until 1954 some had been given alcoholised vaccine and some others had had injections of both preparations at different times. The three groups "phenolised", "alcoholised" and "mixed" were compared on

the basis of the severity of the illness, but no difference could be detected. Each was then compared separately in age-time groups with all uninoculated patients in the corresponding age-groups on the basis of "severity":

(1) For the "phenolised" group, it was found that:

(a) patients who were inoculated between 1910 and 1939 were very significantly more likely to have a mild illness ($P < 0.001$).

(b) patients who were inoculated between 1940 and 1949 showed no significant difference in the severity of their illness from uninoculated patients in the corresponding age-group,

and (c) patients who were inoculated between 1950 and 1963 were significantly more likely to have a mild illness. ($P < 0.005$).

(2) For patients who had either alcoholised vaccine alone or alcoholised plus phenolised vaccines, comparison with uninoculated patients was only possible in the 30-44 year age-group because of the small numbers in other age-groups.

This comparison showed that these inoculated patients were no more likely than uninoculated patients to have a mild illness.

It appears, therefore, that in patients who had received phenolised vaccine during and after the First World War

and after the Second World War, the vaccine had a long-term effect in reducing the severity of the attack of typhoid fever, and that this effect was more marked in patients who had been immunised during the First World War. In patients who were immunised during or immediately after the Second World War, however, whether with alcoholised or phenolised vaccine, immunisation had no significant long-term effect in modifying the course of the illness.

It is believed that an attack of typhoid fever produces a typical secondary antibody response in patients who have been immunised, that is the level of antibody in these patients may be higher than in uninoculated patients. This may occur even when the level of serum antibodies before infection was undetectable (Wilson and Miles 1965). The maximum heights of S. typhi 'H' serum antibodies in inoculated adults were compared with those of uninoculated adults. No difference was found. Within the group of inoculated adults the maximum levels of 'H' antibodies in each patient were compared on the basis of the type of vaccine given, the number of injections, the time since the last injection, and the severity of the illness. No differences were detected in any of the comparisons. It would seem that the maximum level of serum anti-:bodies is largely dependent on individual variation.

DISCUSSION

The effect of immunisation in protecting against an attack of typhoid fever is no longer in doubt, although the duration of this effect is still uncertain. However, its ability to reduce the severity of the illness, once contracted, has not yet been universally accepted. Wright (1902) claimed that immunisation reduced the mortality of the disease by half. Torrens (1923) agreed with this finding and stated that during the First World War "the average case of typhoid fever in a fully protected man is very much less serious, indeed it was difficult, if not impossible, in 1915 to judge clinically in certain cases whether the infection was typhoid or modified by inoculation, or paratyphoid fever". He observed also that in inoculated men who developed typhoid fever the average duration of pyrexia was 3 days less than in uninoculated men and the incidence of complications was greatly reduced.

During the Second World War several outbreaks occurred amongst immunised personnel. Although it was not generally possible to compare the severity of the illness in inoculated and uninoculated men, the impression gained by most observers was that prophylactic inoculation did not affect the course of the illness. Raettig (1944) observed an outbreak affecting 32

inoculated men in the German Army and stated that the course of the disease was severe, complications were frequent, and the case-mortality was 25%. Jordan and Jones (1945) stated that if resistance to attack was overcome the disease produced was just as severe in immunised as in unimmunised individuals, and Anderson and Richards (1951) observed that "the clinical course is not materially influenced by previous immunisation". They found that the severity of the illness was not less in patients who had received a greater number of injections of T.A.B. vaccine.

In the post-war era Rowland (1961) calculated that in 39 immunised patients the severity of the illness was significantly reduced when compared with 486 unimmunised patients, but previous inoculation did not appear to affect the relapse rate or incidence of complications. Ashcroft et al.(1964) stated that 12 of 26 cases (46%) in immunised children were mild as opposed to only 12 of 88 cases (14%) in a control group.

If all these statements are taken at their face value although they are not based on a uniform definition of "severity", it would appear that immunisation is capable of modifying the course of typhoid fever, but did not do so in those immunised during the Second World War.

In Aberdeen a similar conclusion was reached. Moreover, it was observed that patients immunised almost 50 years previously still retained some protection against a severe attack of typhoid fever. It is possible that these patients were more likely to have suffered an undiagnosed or sub-clinical attack of typhoid fever during early life and that this has conferred additional protection. On the other hand, it may well be that vaccine used in the early days of immunisation was more potent than any of the allegedly improved vaccines which have since become available.

It is conceivable that further research with this in mind would produce a vaccine capable of conferring life-long protection against typhoid fever.

C. PROVOCATION TYPHOID

In 1904 Wright stated that "there succeeds in every case upon the inoculation of a vaccine a negative phase, characterised by an impoverishment of the blood in antitropic substances. With this ebb, or negative phase, is associated a phase of increased susceptibility to bacterial infection". Streebe (1928) described 30 cases of "provocation typhoid", that is, typhoid fever magnified by immunisation during the incubation period, and stated that if the illness began within 2 days of an injection of T.A.B. vaccine, the onset was sudden, and the illness severe with intense rigors, whereas if the interval between immunisation and the onset of illness was longer the illness tended to be milder.

Raettig (1950) described 1,702 cases of typhoid fever who were inoculated during the incubation period. He stated that not only was the mortality as high amongst them as amongst the uninoculated, but that the impression was that it was higher, although he did not show statistical analysis to support this claim. It appeared that an injection given during the incubation period hastened the onset of symptoms, and that this

effect was greatest when the injection was the first one of a primary course and least when it was a "booster" inoculation. He confirmed these observations by giving killed vaccine to mice during the incubation period. There was a quicker and greater mortality in the mice, the effect being more marked the later in the incubation period that the vaccine was given (Raettig 1959).

The effect on the course of typhoid fever of giving vaccine to an individual during the incubation period is probably two-fold: first, a decrease in the quantity of protective circulating antibody and, second, an increase in the quantity of circulating endotoxin. When Wright observed a "negative phase" it was in persons in whom serum antibodies were already present (Wright 1904). When bacterial antigen is introduced into serum which contains antibody, some of the antibody immediately combines with the antigen (Smith and Martin 1948). If this occurs during the incubation period of typhoid fever the subsequent reduction in serum antibody levels will decrease the resistance of the host to infection and worsen the disease. The later in the incubation period that this occurs, the more likely is antibody to be already present and available for removal by the newly introduced antigen. It is probable that

the additional endotoxin which is released from the vaccine is sufficient to raise the total amount of circulating endotoxin to a level where the onset of symptoms and fever is precipitated.

There were 4 patients in Aberdeen who were inoculated with T.A.B. vaccine during the incubation period.

The first of these, Patient No.539, was a girl of 20, who ate infected meat on 9th May, 1964. Eleven days later she developed malaise, headache and mild diarrhoea for a week, but serology and cultures of blood, faeces and urine were all negative on two occasions and the symptoms settled. She was immunised on 3rd June in Edinburgh and on the following day she developed severe symptoms of typhoid fever. Blood culture was positive and the illness ran a typical uncomplicated course.

Patient No.495 developed malaise and headache 19 days after eating infected meat; 6 days later she was given T.A.B. vaccine and immediately developed severe headache and fever associated with constip-:ation and profuse epistaxis. Blood and faeces cultures were positive. She had a typical uncomplicated illness. This patient showed S. typhi 'H' agglutination only, to a level of 1:25 dilution until 6 months after discharge, when it reached 1:3200 dilution.

A third patient, No. 481, was immunised by sub-:cutaneous injection 27 days after eating infected food. She had a marked febrile reaction with rigors which persisted for 8 days, and a very severe local reaction which persisted for the same length of time. Faeces culture was positive

although blood culture was negative; her temperature settled spontaneously. Serum agglutination in this patient showed maximum S. typhi 'H' agglutinins at 1:25 dilution and no 'O' antibodies, but agglutination with S. paratyphi B H at 1:800 dilution.

Patient No.105 was immunised 10 days after eating infected food. She had a typical response, that is, fever and malaise which failed to settle, and she developed constipation. She had a brisk epistaxis 2 days later. Clot culture was positive 7 days after immunisation; she responded well to chloramphenicol but continued to excrete S. typhi in faeces during the first week of convalescence.

At least three of these patients demonstrated the effect of immunisation in precipitating the onset of illness when the immunisation was performed during the incubation period.

SECTION V

ASYMPTOMATIC TYPHOID FEVER

Asymptomatic typhoid fever is of great importance since it may result in typhoid carriers who are never suspected. Its occurrence and probable aetiology are discussed in this section on the basis of previous findings and of symptomless cases of typhoid excretion and bacteraemia discovered in Aberdeen.

ASYMPTOMATIC TYPHOID FEVER

For many years it has been known that typhoid bacilli could be isolated from either the excreta or the blood of persons who were not ill. Symptomless excreters of *S. typhi* may be divided into three categories:-

(i) "Precocious" or incubatory excreters, that is, persons who later become ill.

(ii) Healthy excreters, that is persons who never suffer any overt illness.

(iii) Carriers, that is, persons who continue to excrete *S. typhi* for variable periods after suffering from acute typhoid fever.

Only the first two categories will be discussed in this section. A further type of symptomless typhoid infection - bacteraemia - will also be studied.

A. ASYMPTOMATIC TYPHOID EXCRETERS

(i) "Precocious" carriers

Ledingham and Arkwright (1912), discussing diphtheria, said that "by a precocious carrier is meant a person in whom *Bact. diphtheriae* is found for a longer or

shorter time, without any symptoms of disease appearing, but who eventually develops diphtheria".

J. Conradi (1907) was the first to report the presence of typhoid bacilli in the excreta before the onset of overt infection. Klinger (1909) found such carriers when he tried to discover at what stage a case of typhoid fever was most likely to cause secondary cases. He discovered that of 812 contact infections 33 arose from persons in the first, and 150 from persons in the second, week of incubation, that is, the originating cases were excreting S. typhi at these times. In the Oswestry outbreak in 1948, 15 of the 135 cases were diagnosed by stool culture during the incubation period (Jones 1951).

In Aberdeen, 10 patients examined as contacts were found to be excreting during the period of incubation. Specimens were taken at 2 - 3 day intervals, but only in five cases is it known approximately when excretion began, since the remainder had a positive isolation at the time of the first examination and may have been excreting for a variable time beforehand. Details of these patients are shown in Table 33.

TABLE 33

CASES OF TYPHOID FEVER DIAGNOSED DURING THE INCUBATION PERIOD

No.	Sex	Age	Length of Incubation Period (I.P.)	Day of I.P. on which 1st specimen taken	Day of I.P. on which 1st specimen positive	No. of days between 1st positive specimen & onset of illness	Remarks
25	M	63	19	16	16	3 *	Moderate illness
340	F	82	24	22	22 X	2 *	Relapse
471	F	26	19	15	15	4 *	Relapse
473	M	57	28	12	27	1	Mild illness
354	F	19	27	25	25	2 *	Convalescent excreter
476	M	33	31 ?	? 7	? 27	4	Mild illness
324	M	10	22	14	16	4	Convalescent excreter
193	F	45	22	21	21	3 *	Convalescent excreter
205	F	59	22	19	21	3	Mild illness
509	F	38	25	20	23	2	Relapse

* = UNCERTAIN

X = URINE ALSO POSITIVE.

Although the incubation periods of these patients are longer than usual, this is inevitable since only such patients had time to be examined as contacts. Patient No.476 ate infected food on two occasions, therefore his incubation period is uncertain, but has been taken as the shorter of the two.

No patient was known to excrete for more than 4 days before the onset of clinical illness. Precocious carriers have, however, been found who excreted S. typhi for several months before developing typhoid fever. Battlehner (1910) reported four cases where typhoid bacilli were excreted for periods ranging from 21 to 117 days before the onset of fever, and Wilson (1938) discovered a patient in a mental hospital who excreted for $4\frac{1}{2}$ months and caused 10 secondary cases before he developed a severe attack of typhoid fever. No such late cases have been found in Aberdeen within a year after the outbreak.

(ii) "Healthy" Excreters

Many "healthy" excreters have been reported since Von Drigalski and Conradi first found 4 such cases in 1902. Scheller (1908), during the anti-typhoid campaign in South-West Germany, found that of 72 people who drank infected milk over a period of some months, 40 did not contract overt typhoid fever;

but 18 of the 40 excreted bacilli in stool or urine for variable periods. Those individuals who showed bacilli in urine may indeed have had a symptomless bacteraemia, but it is perhaps more probable that this was merely contamination.

Klinger (1909) in the same campaign, found that 119 of 211 temporary carriers (56%) had no history of typhoid fever, while Scott (1915) in Jamaica found typhoid bacilli at autopsy in the gall-bladders of 6 out of 200 individuals with no history of typhoid fever. However, typhoid fever was endemic in both these areas and these incidences of healthy excreters may be higher than is found where typhoid is epidemic.

The duration of excretion of typhoid bacilli in healthy people may vary considerably: Fornet (1912) found that excretion in 78 of 187 healthy people persisted for months and even years, whereas Klinger (1906) found that of 11 such excreters 9 gave positive isolations on only one occasion despite repeated testing, and all were negative after a fortnight. It is possible that Fornet's cases had unobserved mild symptoms, since Klinger's finding appears to be more usual and has been better supported even since the introduction of selective media. These media make it possible to obtain positive isolations from persons who

excrete only a few bacilli, and by this method fewer healthy excreters are likely to be missed. Rays (1948) found 5 excreters amongst healthy people who had been in recent contact with cases of typhoid, and she noted that in each instance the bacilli were isolated only in a single faeces specimen, despite repeated testing. All 5 persons had been inoculated a year previously but all had negative serum 'H' agglutinins and 'O' agglutinins of nil or 1:50. This agrees with the observation of Forster and Kayser (1905) that the concept of a transitory alimentary infection was supported by the fact that the serum of persons who harbour the organism as a saprophyte in the intestine without suffering from the disease seldom shows any agglutinating power.

It has been suggested that one isolation alone may be due to a labelling or laboratory error, but this is unlikely to account for the number of cases mentioned above. At Oswestry 6 of 19 symptomless excreters had only a single positive specimen (Jones 1951) and these cases occurred in a hospital community where risk of contamination of specimens was negligible.

There were 14 healthy excreters in Aberdeen and a further 4 with minimal symptoms, namely: headache or malaise or slightly

loose stool for 1 - 2 days. (Appendix V, 1a.) The age distribution of these 18 patients was not significantly different from that of the 469 typhoid cases, but there were more men than expected. Six of the men had been immunised and one woman: this was no more than expected when compared with patients who had overt illness.

B. SYMPTOMLESS TYPHOIDAL BACTERAEMIA

Symptomless typhoidal bacteraemia was recorded in 1907 by H. Conradi, who during an epidemic found typhoid bacilli in the blood of 3 healthy carriers. Ebeling (1914) reported the rather surprising finding of bacteraemia on one occasion in a woman who was suspected of being a healthy carrier. Repeated stool and urine specimens were negative over a period of several months and she never became ill; at the time that blood culture was positive she had serum agglutinins of 1:200. Marmion (1952) reported two cases of afebrile bacteraemia, one in a completely afebrile illness, the other late in convalescence.

Snyder et al.(1964) have reported fully two cases of

asymptomatic typhoid bacteraemia (Figure 16). They fed 64 volunteers with 10 or more $I.D._{50}$ doses of S. typhi 'phage type 'D', isolated from a carrier during cholecystectomy. Seven men failed to develop typhoid fever, but 2 of these 7 were shown to have bacteraemia during the period when clinical illness usually occurs. One man had positive blood cultures from 4 to 14 days after infection, the only clinical feature being a mild pyrexia from the 10th to 12th days; stool culture was negative after the first post-infection day. The second man gave a positive blood culture only on the 8th day after infection, stool culture being positive on the 1st and 11th days. He, too, had a mild intermittent symptomless pyrexia during the 1st to 12th days.

There were 4 patients in Aberdeen with symptomless bacteraemia; their laboratory findings are shown in Table 34. One other patient had a positive blood culture during convalesc-:ence, 6 days after the end of a "post-treatment pyrexia" and during a course of ampicillin. The positive isolations in 3 of the 4 cases discussed here were obtained by clot culture.

The fourth patient, No. 348, was also a symptomless excreter; he gave a positive faeces specimen on 1st June, 1964 and had a positive blood culture

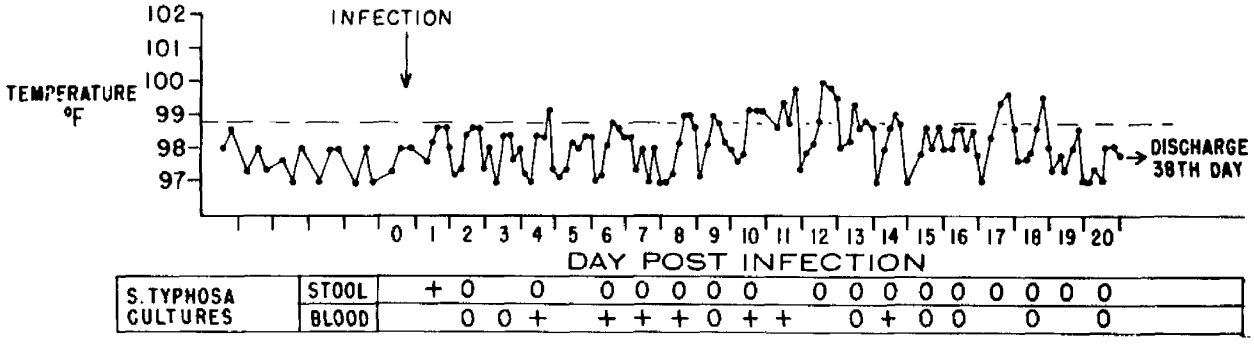


FIG. 16A.

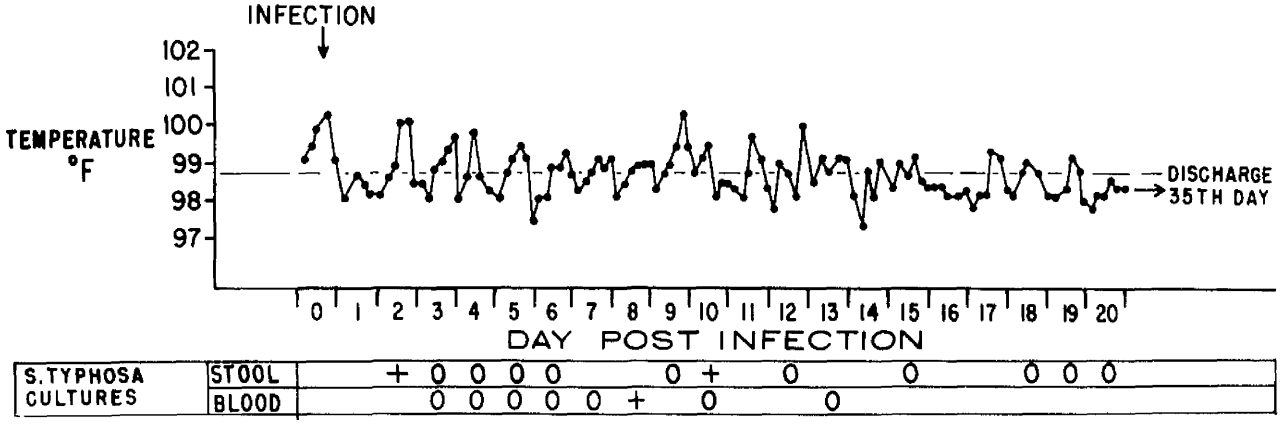


FIG. 16B

THE CLINICAL COURSE OF TWO VOLUNTEERS WHO SUFFERED ASYMPTOMATIC TYPHOID BACTERAEMIA

SOURCE: SNYDER ET AL. 1964

TABLE 34

LABORATORY FINDINGS IN FOUR CASES OF SYMPTOMLESS BACTERAEMIA

No.	Sex	Age	Date of Infection	Interval from Infection to Positive Culture (days)	Number of Positive Isolations	Date	Serum Agglutination			Max. Temp. °F	Date of last T.A.B. Injection
							S. typhi "H"	S. typhi "O"	S. typhi Vi.		
57	F	57	?	?	1	30.5.64	NIL	-	-	99.0	NIL
						10.6.64	NIL	NIL	NIL		
						19.1.65	NIL	NIL	1:40		
43	M	51	?	?	1	30.5.64	-	-	-	98.6	1948
						16.6.64	-	NIL	1:10		
						19.1.65	-	NIL	1:20		
123	F	24	?	?	1	8.6.64	-	-	-	98.2	NIL
						13.6.64	-	NIL	NIL		
						2.2.65	-	1:50	NIL		
348	M	60	22.5.64	15	1	6.6.64	-	-	-	100.0	NIL
						11.6.64	-	-	-		
						30.6.64	-	NIL	1:10		
						4.2.65	-	NIL	1: 5		

on 6th June, 1964 at which time a stool specimen was negative. No further specimens were positive; this suggests that the isolation of bacilli from faeces in this patient was obtained during the "incubation period" preceding a silent bacteraemia.

C. DISCUSSION

The mechanism of host-resistance to infection has been discussed in Section I. When the typhoid bacillus is ingested one of four things may happen:-

(a) it may be quickly and completely excreted in faeces.

(b) it may immediately invade the blood stream of the host via the lymphatic system of the intestinal canal, whence it may or may not cause overt illness.

(c) it may live a saprophytic existence in the gut for a variable length of time, after which it is overcome by host-resistance and other organisms and is completely destroyed or excreted.

(d) it may exist as a saprophyte for a period of time and then multiply sufficiently to invade the host and cause generalised infection.

It is probable that this last alternative is the explanation of precocious carriers, overt illness occurring when the organism has multiplied sufficiently to invade the host.

In excreters who do not become ill, any of the first three events may occur, thus:-

(a) those in the first category excrete S. typhi immediately after ingestion of the organism for a short period of time only. This occurrence was not demonstrated in Aberdeen, although it might be inferred in the woman who had diarrhoea immediately after eating suspect food and did not become ill. (see page 75).

(b) In the event of invasion, bacteraemia occurs but is symptomless; the organisms may be totally destroyed in the tissues or some may be re-excreted. The latter occurred in the second of Snyder's patients with symptomless bacteraemia (Figure 16).

(c) the most likely explanation of most symptomless excreters is the existence of the organism for a time as a commensal in the gut and then its total excretion without generalised invasion of the host.

In this last type of infection, there should be no

antibody produced since the organisms do not reach the local lymphoid tissues, which are believed to be the site of antibody formation. But if, as Madsen believed, some organisms do reach the local lymphatic glands but are held there by a "blockade", these organisms, even if they are but few, will provide localised antigenic stimulus and low levels of serum antibodies may be detected.

Examination of the serological findings in the symptom-:less excreters in Aberdeen at first showed no uniform pattern. However, two of these patients had signs of generalised infection, that is, rose spots or splenomegaly (Patients No. 174 and 252) and one of the two had diagnostic levels of S.typhi 'H' serum agglutinins. The other (No.252) was a child from whom it was difficult to obtain a sample of blood, and since the diagnosis was confirmed bacteriologically no specimen of blood was taken until his discharge from hospital. Thus, in one at least of these two patients the serological findings, combined with the physical signs, suggest that she did in fact have symptoms which were ignored or forgotten.

Of the remaining symptomless excreters, 5 had no demonstrable 'H' or 'O' serum antibodies and 11 had maximum 'H'

serum agglutination at 1:200 dilution in the inoculated and 1:100 dilution in the uninoculated patients. These levels are appreciably lower than those of patients with overt illness in whom the mean maximum agglutination titre in the uninoculated was 1:291 with a mode of 1:800. These agglutination titres support the view that in symptomless excreters the bacteria, if they reach a site of antibody formation, do so only to a slight and possibly localised extent.

The 4 patients in whom symptomless bacteraemia occurred, one of whom was also a symptomless excreter, also showed no 'H' or 'O' serum antibodies at the time of infection. Snyder et al.(1964) suggested that in such cases the organisms are held intracellularly within phagocytes and destroyed there, and are therefore not available either to act as an antigenic stimulus or to release sufficient quantities of circulating endotoxin to produce overt illness. It is not certain, however, whether this phenomenon is attributable to an unusual feature of the pathogen or to exceptional resistance in the host.

CONCLUSIONS:

Examination of the serological findings in 18 patients with symptomless typhoidal excretion supports the premise that

the bacteria are usually contained within the lumen of the gut or held at the local lymphatic glands in such cases.

The absence of serum agglutination in 4 patients with symptomless bacteraemia may be explained if the bacteria reside wholly intracellularly.

SECTION VI

ANTIBODY PRODUCTION IN TYPHOID FEVER

There is a wide variation in the levels of antibodies found in serum in different typhoid patients. The difficulties of interpreting the results of serological antibody assays are indicated and an attempt is made to correlate the nature of the measured antibody response with the course of the disease and its treatment in different groups of patients.

A. THE ESTIMATION OF ANTIBODY RESPONSE

(i) Widal's Reaction

In 1896 Widal recorded the fact that the serum of a typhoid patient will agglutinate typhoid bacilli. He developed this as a test for typhoid fever and used it quantitatively by noting agglutination at different dilutions of serum. Felix, after he and Weil had described in 1920 the two different antigens 'H' (or flagellate) and 'O' (or somatic), proceeded in 1930 to elaborate Widal's reaction as a qualitative test which identified separately these two antigens. The test nowadays includes S. paratyphi A. and B. and may also include other organisms, but unless otherwise stated its mention in this section refers only to S. typhi.

The interpretation of Widal's reaction is sometimes difficult. In a person who has not received T.A.B. vaccine, and has not suffered previous typhoid fever, the presence of serum antibodies to the flagellar or 'H' antigen, even in low titre, is indicative of typhoid fever, but somatic or 'O' antibodies may occasionally be found in uninfected or uninoculated

persons (Anderson and Gunnell 1964). Vi antibody estimation is not of value in diagnosis of the acute illness, but has been claimed to be helpful in identifying the carrier state (Report of Ministry of Health 1945). The interpretation of Vi antigenic response is at present the subject of further research in Aberdeen and will not be dealt with in this thesis.

In a person who has received T.A.B. vaccine in the past, interpretation of serological results is much more difficult. It is considered that a two-fold rise in serum titre of S. typhi 'H' antibodies is essential before a diagnosis of typhoid fever may be substantiated by this means. Even then this rise may be due to an anamnestic reaction, that is, the production, in response to a non-specific pyrogenic stimulus, of specific antibodies previously produced either by infection or by inoculation. 'H' antibodies, therefore, are unreliable in the previously inoculated. 'O' antibodies, with the few exceptions found in healthy persons, appear only in the face of recent infection, except in the recently inoculated. However, they may not differentiate between typhoid and paratyphoid fevers, regardless of the immunisation state of the individual (Felix 1930). Thus, as happened in Aberdeen, typhoid fever may produce S. paratyphi B 'O' antibodies but none to S. typhi.

For practical purposes, agglutination reactions may be interpreted thus:-

> In the uninoculated person, 'H' antibodies are proof of infection, but are of no value in the inoculated;
>
> 'O' antibodies are of more value than 'H' in the previously inoculated, provided that only either typhoid or paratyphoid is suspected. If a differential diagnosis is required, 'O' antibodies are unreliable.

Widal's reaction, therefore, is equivocal evidence and must be considered in conjunction with clinical and bacteriological findings.

(ii) Time of appearance of Serum Antibodies

It is generally believed that a diagnostic level of serum antibodies is rare before the 10th day of untreated illness (Top 1964) and that somatic antigens appear before flagellar (Felix 1930). However, at Oswestry in 1948 Jones found that diagnostic 'H' and 'O' titres were found from the 1st to the 6th day of illness in the serum of the first 10 cases.

It will be shown that similar Widal reactions were found in the first 10 patients in Aberdeen; both outbreaks were caused by the same 'phage-type of S. typhi.

Several authors have investigated the percentage of patients with positive agglutination reactions in successive weeks of illness; 2 sets of results are shown in Table 35. Neither observer, however, continued the series beyond the 5th week of illness. The persistence of antibodies after the end of the acute illness may vary considerably, regardless of the carrier state. Felix (1930) found 'H' but no 'O' agglutinins in persons who had recovered from typhoid some years previously, while Vogelsang (1950) examined the sera of 10 patients who had recovered from typhoid fever 1 year or more previously and found that 8 gave 'H' agglutination at 1:20 to 1:80 dilution, and 3 gave 'O' agglutination at dilutions of 1:20 to 1:40. In Aberdeen, as will be shown, some patients produced their maximum antibody response more than 6 months after the end of the acute illness.

(iii) Variations in Antibody Response

1. Absence of serum antibody response

This phenomenon has been reported by several writers. Huckstep (1962) described two cases with no serum anti-

TABLE 35

RATE OF OCCURRENCE OF POSITIVE AGGLUTINATION REACTIONS IN SUCCESSIVE WEEKS OF ILLNESS

WEEK OF ILLNESS	PERCENTAGE POSITIVE AGGLUTINATION REACTIONS					
	1	2	3	4	5	AVERAGE—
GAY (1918)	61	82	87.5	92	100	91.8
PARK AND WILLIAMS (1925)	20	60	80	90	75	88

:bodies; one relapsed, the other had an intestinal perforation. Kostic (1963) found that 17 of 144 treated patients (11.8%) showed no antibody response, while Lantin (1963) found that 5 of 28 patients who relapsed had no serum agglutinins before relapse and 3 of these 5 had none at any time. The reasons for this failure to produce antibodies will be discussed later.

(iii) 2. Non-specific response

This differs from an anamnestic reaction in that it is a cross-reaction produced by an antigen of a similar bacterium to the one being tested. This phenomenon was noted by Gay (1918) who observed that the serum of a case of typhoid fever would agglutinate the paratyphoid bacillus and also, less frequently, that the reverse could occur. This is explained in the Kauffman-White scheme of antigenic notation, where it may be seen that the S. typhi 'O' antigen XII is common to several of the Salmonella group, including S. paratyphi B and C . (Report of Salmonella Sub-committee 1934).

It was a notable feature of the Aberdeen outbreak that 'O' antibodies were more commonly found to S. paratyphi B than to S. typhi, at least in serum estimations performed on admission to hospital.

In addition to these factors, it should be remembered that the level of circulating antibody in serum is not necessarily a true indication of the level of immunity in the tissues. If the theory of "cellular immunity" is correct and it does depend on cell-bound antibody (see page 46) then sero-:logical antibody assays may reflect only a small part of the quantity of active antibody present in the host. Similarly, it has been demonstrated clearly during the assessment of the effect of T.A.B. vaccine that the presence of circulating anti-:body is by no means satisfactory proof of active immunity.

B. THE ESTIMATION OF ANTIBODY RESPONSE TO INFECTION IN PATIENTS IN ABERDEEN

(1) Source of Data

Agglutination tests were done initially in all cases with suspected symptomatology and on all known contacts of suspect cases. A full Widal reaction was done in the first cases but increased pressure of work in the laboratory made it impossible to continue with this, and a modified Widal test for antibodies to S. typhi 'H' only was then performed. The

omission of the estimation of S. typhi 'O' agglutinins was based on: (i) the length of time this takes, and (ii) the failure of many of the early cases to produce 'O' agglutinins. At first 'H' agglutinins were measured in dilutions of 1:25, 1:50, 1:100 and so on, serially to 1:1600, but this was later reduced to a maximum dilution of 1:400, since this permitted three times as many sera to be tested at once. Patients who were admitted to hospital before their serum was tested had an abbreviated Widal reaction test done on admission. Further tests were usually done in hospital:

(i) when the diagnosis was in doubt,

(ii) when no reaction was found at first examination,

and (iii) on relapse.

All patients had full Widal and Vi-agglutination estimations performed on discharge from hospital. It was decided also that all patients should be asked to attend for serum agglutination estimations at 3, 6, 12 and 24 months after discharge from hospital; the results in those patients who attended at 3 and 6 months are included here.

(ii) Serological response related to the duration of the Illness

The first 10 patients admitted had much higher levels of serum 'H' agglutinins than is normally expected within the first week of illness, as shown in Table 36.

Here, as in Oswestry, later cases were more "classical" in having a slower appearance of antibodies in serum. Of 376 patients who had not previously been inoculated, 117 had no measurable 'H' antibody on admission; their mean day of clinical illness at that time was 4.5. At the other end of the scale, 45 of these uninoculated patients had S. typhi 'H' titres at over 1:400 dilution on admission with a mean day of clinical illness at that time of 9.5. The level of 'H' antibodies on admission related to day of clinical illness in inoculated patients showed no constant pattern (See Figure 17).

(iii) Diagnostic Widal Reactions

The "diagnostic Widal reaction" was taken to be the first serum assay in each patient which showed a diagnostic level of agglutination. In many cases the diagnostic Widal reaction was the one done on admission to hospital. Where more than one serum assay was performed, either before or shortly after admission, the diagnostic Widal reaction was taken to be

TABLE 36

SEROLOGICAL FINDINGS IN THE FIRST TEN CASES

No.	Sex	Age	Date	Day of Illness	Date of last T.A.B Injection	Titre of Agglutination			
						S.Typhi 'H'	S.Typhi 'O'	S.Paratyphi B.'H'	S.Paratyphi B.'O'
267	F	19	17.5.64	3		1:2560	NIL	1:25	1:320
292	F	18	18.5.64	3		1:5120	NIL	NIL	NIL
282	M	37	18.5.64	5	1952	1:50	1:200	NIL	1:400
172	M	11	19.5.64	5		1:1600	NIL	NIL	1:100
50	F	33	19.5.64	5		1:6400+	1:3200+	NIL	1:100
6	F	43	20.5.64	5		1:1600+	NIL	NIL	1:50
52	F	10	20.5.64	6		1:1600+	1:800	NIL	NIL
49	F	3	20.5.64	3		1:1600+	1:400	NIL	NIL
51	M	32	20.5.64	5	1952	1:1600+	1:400	NIL	NIL
278	F	7	20.5.64	5		1:1600+	1:50	NIL	NIL

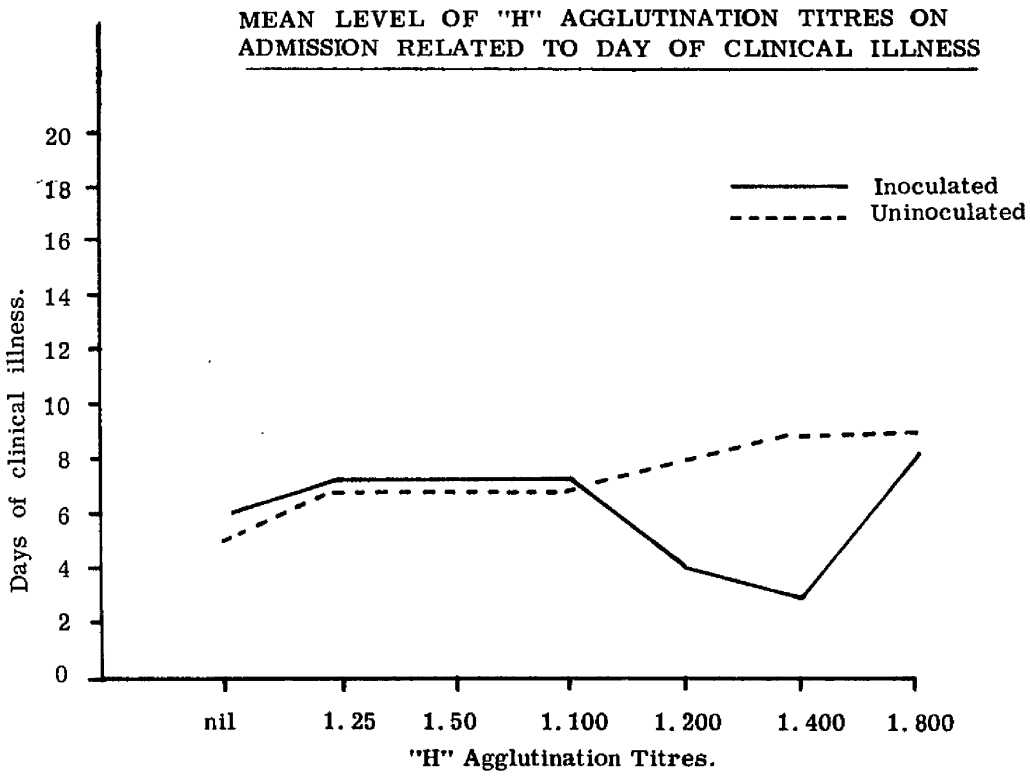


Fig. 17 - Mean Level of 'H' Agglutination Titres on Admission to Hospital, related to day of Clinical Illness.

the one in which the highest level of agglutination occurred.

With regard to serum 'O' antibodies, the strong impression was received that, except for the first few cases admitted, few patients had demonstrable levels of agglutination. Of 89 sera tested for S. typhi 'O' antibodies, only 8 (9%) showed agglutination, whereas 75 (61%) of 134 sera tested for S. paratyphi B 'O' antibodies showed agglutination. These figures are not necessarily representative, however, since the remainder of the patients in the outbreak had only S. typhi 'H' antibodies estimated for diagnostic purposes.

'H' antibodies were estimated in the sera of all patients. Of these, 76 showed no 'H' agglutination despite repeated testing. The remainder gave agglutination at levels between 1:25 and 1:6,400+ dilutions.

(iv) Discharge Widal Reactions

'H' antibodies were again seen to be more in evidence than 'O' antibodies, in the discharge Widal reactions; only 55 of 465 sera tested showed 'O' agglutination, and in 32 of these the level was only 1:25 or 1:50 dilution. When 'H' and 'O' antibody levels were considered together for each patient on discharge, the results were as follows:-

(a) 139 patients showed no 'H' or 'O' antibodies to S. typhi on discharge

(b) 128 patients showed either 'H' or 'O' antibodies, or both, to S. typhi at dilutions of 1:25 or 1:50 on discharge

(c) 198 patients showed either 'H' or 'O' antibodies, or both, to S. typhi at dilutions of 1:100 or above.

The majority of these sera were taken at approximately 5 weeks from the date of onset of illness.

(v) Widal Reactions at 3- and 6-months Follow-up Examinations

There were some defaulters at the follow-up clinics, but the pattern of antibody production was clear, namely that with successive tests increasing numbers of patients showed no antibody response. One interesting feature is that at 6-month follow-up the sera of 104 patients showed 'O' antibodies, as compared with 40 at 3-month follow-up; that is, an increase of 18% of the total number of tests performed. The reason for this is uncertain, but it may be due to a variation in standard suspension. It is known to the author that factors which might affect agglutination are being studied in the laboratory as part of a research project.

(vi) Assessment of the Overall Antibody Response in Different Groups of Patients

In an attempt to assess the level of antibody production in each patient, all Widal reactions in each were considered together, that is, diagnostic and discharge Widal reactions, and all other estimations which were performed during the course of the illness and for 6 months after discharge from hospital.

'H' and 'O' antibodies were considered together for each individual reaction and the higher level was taken as representative of that reaction.

For this purpose those patients who showed S. paratyphi B 'O' antibodies instead of antibodies to S. typhi 'O' were classified according to the level of the former in the same way as those patients who showed S. typhi 'O' agglutination. An arbitrary distinction between "minimal" and "normal" response was made in order to assess a possible difference in the characteristics of patients who showed varying levels of response.

Four groups of patients were studied:-

(1) Patients with no antibody response at any time

that is, patients who showed no serum antibodies either beforem during or after their stay in hospital.

(2) Patients with "minimal" antibody response

that is, patients who showed serum antibodies, 'H' or 'O', at 1:25 or 1:50 dilution in some or all specimens of sera tested before, during or after their stay in hospital.

(3) Patients with "normal" antibody response

that is, patients who showed 'H' or 'O' serum antibodies at 1:100 dilution or above at any time.

(4) Patients with delayed antibody response

that is, patients whose level of serum agglutination was highest at 3 or 6 months after discharge from hospital. For this purpose only a rise of more than one dilution was accepted.

1. Characteristics of patients who showed no serum antibodies

There were 35 patients in whom serological assays were completely negative before, during and for 6 months after their stay in hospital (see Appendix VI.1a) There are several possible reasons for the absence of antibody

production in typhoid infections:-

(1) The infection may be localised to the intestine and be unable to act as an antigenic stimulus.

(2) Although generalised infection occurs a small infecting dose or a mild illness may provide insufficient antigen to produce measurable levels of serum antibody.

(3) The effect of early chloramphenicol therapy on antibody production has already been discussed in connection with the cause of relapse.

Kostic (1963) found that in 11 of 17 patients who showed no serological response chloramphenicol therapy was started between the 6th and 10th days of illness.

(4) Relapse is known to occur in the face of high levels of antibody, but this may be an unusual finding and patients with no circulating antibody may be more likely to relapse.

(5) It is generally accepted that the young and the very old show a slower and less effective

resistance to infection; this might be demonstrated by poor antibody response.

(6) Since the mechanism of antibody production is known to be influenced by many factors other than the presence of specific antigenic stimuli, it may be that there is no one reason for absence of response, and in the present state of our knowledge it would, therefore, be attributed to "chance".

All but 5 of the 35 patients who showed no serum anti-:bodies had either proved bacteraemia or evidence of generalised infection, that is, rose spots or splenomegaly. The 35 patients were compared with 295 patients who showed "normal" antibody response to infection. The results of these comparisons are shown in Table 37. There was no demonstrable difference in the age and sex distribution of the two groups, nor in the distribution of immunised patients and the incidence of convalescent excretion was the same in each group. However, there were very significantly more patients with a mild illness who showed no antibody response ($x^2 = 12.84$ $P < 0.00050$) and fewer patients who relapsed in this same group ($x^2 = 4.77$ $P < 0.05$).

With regard to antibiotic therapy, there was no difference in the type of initial treatment between patients with

TABLE 37

COMPARISON OF PATIENTS SHOWING NO ANTIBODY RESPONSE WITH PATIENTS SHOWING "NORMAL" RESPONSE

FACTOR	CASES COMPARED	SIGNIFICANT DIFFERENCE PRESENT
1. AGE DISTRIBUTION	ALL PATIENTS SHOWING "NORMAL" ANTIBODY RESPONSE	No
2. SEX DISTRIBUTION		No
3. INCIDENCE OF RELAPSE		Yes
4. INCIDENCE OF CONVALESCENT EXCRETERS		No
5. DISTRIBUTION OF "SEVERITY OF ILLNESS"		Yes
6. INCIDENCE OF IMMUNISED PERSONS		No
7. TREATMENT WITH CHLORAMPHENICOL:		
A. MEAN DAILY DOSE	ALL PATIENTS SHOWING "NORMAL" RESPONSE, WHO RECEIVED CHLORAMPHENICOL	No
B. MEAN DURATION OF TREATMENT		No
C. DURATION OF ILLNESS BEFORE TREATMENT		No
D. DURATION OF PYREXIA ON TREATMENT		No
8. NUMBER OF PATIENTS NOT TREATED	ALL PATIENTS SHOWING "NORMAL" ANTIBODY RESPONSE	No

no antibody response and those with "normal" antibody response, and there was no difference in the dosage, duration and effect on pyrexia of chloramphenicol between the two groups. The mean day of illness at the beginning of treatment was 5.8 days in patients who produced no measurable antibody, as opposed to 7.5 days in other patients, but this difference was no more than could have occurred by chance.

Thus the only obvious factors which distinguished patients who showed no antibody response were their relapse-rate and the severity of their illness. These patients were much less severely ill than other patients and less likely to relapse. It is clear, however, that the absence of serum agglutination does not preclude the presence of infection.

2. Characteristics of patients who showed "minimal" antibody response to infection

There were 101 patients who had serum agglutinins to 1:25 or 1:50 dilutions only at any time until 6 months after discharge from hospital. It seemed possible that these patients might be affected by the same factors as patients who showed no serum agglutination, but to a lesser degree and they were, there-

:fore, compared with patients who showed "normal" antibody response for the same factors as were used in the previous comparison. It was found that there were no significant differences between patients who showed "minimal" antibody response and those with "normal" response.

3. Characteristics of patients who showed delayed antibody response

There were 28 patients who produced their highest level of serum antibodies after discharge from hospital; 9 of them had previously shown no antibody response. The details of these patients are listed in Appendix VI.3a.

It was thought that this delayed reaction might be due to several factors:-

(1) There might be prolonged suppression with anti-:biotic therapy, that is, these patients might have had more than one course of treatment. If this were so this group would include patients who relapsed and sometimes those who continued to excrete S. typhi after the end of the acute illness, since these factors made them liable to have a second or third course of treatment.

(2) Relapse and convalescent excretion might also be the direct cause of the late production of antibody, since the presence of bacteria persisted for longer than in other patients.

(3) There might be a slow reaction to infection due to extremes of age, that is, the very young and the very old.

The 28 patients in this group were compared with 295 patients with "normal" antibody response. A summary of the results is shown in Table 38. It may be seen that there was no significant difference in the age and sex distribution of the two groups, nor in the incidence of immunised individuals. There was no difference in the incidence of convalescent excreters or relapse in those patients with maximal response after discharge. There was no difference in the distribution of "severity of illness", nor in the schedule of or response to treatment. The mean day of illness at the beginning of treatment was 6.8 days in the group under consideration, as opposed to 7.4 days in other patients, but this difference was not significant. There was no difference between the 2 groups in the incidence of patients who were not treated or who were treated either initially or during convalescence with ampicillin. There was, however, a possibly significant excess of patients with delayed response who had more than one course of antibiotic therapy at any time ($x^2 = 4.88$ $P < 0.05$).

TABLE 38

COMPARISON OF PATIENTS WHO SHOWED DELAYED ANTIBODY PRODUCTION WITH PATIENTS WHO SHOWED A "NORMAL" RESPONSE

FACTOR	CASES COMPARED	SIGNIFICANT DIFFERENCE PRESENT
1. AGE DISTRIBUTION	ALL PATIENTS SHOWING "NORMAL" ANTIBODY RESPONSE	No
2. SEX DISTRIBUTION		No
3. INCIDENCE OF RELAPSE		No
4. INCIDENCE OF CONVALESCENT EXCRETERS		No
5. DISTRIBUTION OF "SEVERITY OF ILLNESS"		No
6. INCIDENCE OF IMMUNISED PERSONS		No
7. TREATMENT WITH CHLORAMPHENICOL:		
A. DAILY DOSE	ALL PATIENTS SHOWING NORMAL RESPONSE, WHO RECEIVED CHLORAMPHENICOL	No
B. DURATION OF TREATMENT		No
C. DURATION OF ILLNESS BEFORE TREATMENT		No
D. DURATION OF PYREXIA ON TREATMENT		No
8. NUMBER OF PATIENTS NOT TREATED	ALL PATIENTS SHOWING NORMAL ANTIBODY RESPONSE	No
9. NUMBER OF PATIENTS TREATED INITIALLY WITH AMPICILLIN	ALL TREATED PATIENTS SHOWING NORMAL ANTIBODY RESPONSE	No
10. NUMBER OF PATIENTS TREATED WITH LONG-TERM AMPICILLIN		No
11. NUMBER OF PATIENTS WHO HAD MORE THAN ONE TREATMENT		Yes

Thus, it appears that patients who show maximal serum agglutination late in convalescence are not necessarily still infected. It is possible that this delayed reaction is due to prolonged antibiotic therapy during the acute illness.

CONCLUSIONS:

There were 35 patients who had no detectable serum agglutination throughout the period of illness and convalescence. These patients on the whole were much less severely ill than patients who showed a "normal" response, and were less likely to relapse.

Of 28 patients who showed a delayed antibody response more than expected had received prolonged antibiotic therapy during the acute illness and convalescence.

SECTION VII

THE TYPHOID CARRIER

In this section the incidence and treatment of typhoid carriers up to the present time are described and a classification of carriers is outlined. The aetiology of the carrier state and the possible sites of persistent bacteria are discussed. A clinical trial of ampicillin was conducted in convalescent excreters in Aberdeen; this and the further use of ampicillin in temporary carriers are described. Details are given of both temporary and chronic carriers in Aberdeen.

A. THE CARRIER STATE

In 1891 Chantemesse and Dupre each demonstrated typhoid bacilli in the diseased stone-containing gall-bladder of a patient, both of these patients having had an acute attack of typhoid fever 8 months previously. Other workers confirmed these findings. Lazarus (1895) found typhoid bacilli in the faeces of a patient 41 days after the temperature bec me normal and Von Drigalski and Conradi in 1902 found them in the faeces of four healthy contacts of typhoid patients. In 1902 Koch convinced most physicians of the importance of the carrier state as a reservoir of infection in a community and of the necessity of taking certain public health measures to isolate, and if possible to cure, persons who were carriers.

(i) The Incidence of Typhoid Carriers

Garbat (1922) examined 164 typhoid patients in an American prisoner of war camp during the first world war. He found that 53 (32%) continued to excrete *S. typhi* after the temperature became normal; 17.5% excreted for 1 month, 8% for two months and 4% for three months or more. Browning *et al.* (1933) stated that 2% - 5% of all typhoid patients become permanent carriers, and Leff (1957) confirmed this figure. Vogelsang and Boe (1948) found a

chronic carrier rate of 3% as did Garbat (1922) and Gray (1938).

(ii) Treatment

(i) Conservative.

Various attempts were made to cure the carrier state by chemotherapy, e.g. by altering the intestinal flora with milk soured by lactic acid bacilli and by using calomel and phenol derivatives (Ledingham and Arkwright 1912), but none of these was successful. Vaccine therapy, first suggested by Koch in 1902, was also tried but was of no value (Browning et al 1933). With the advent of antibiotics, in particular penicillin and later chloramphenicol, these drugs were also used, but were unable to cure the carrier state. Until recently, surgical treatment was the only possible cure available.

(ii) Surgical.

The gall bladder was known to be a site of typhoid bacilli during convalescence, and cholecystectomy at first seemed to be the operation of choice. Grimme (1908) found it successful in one case. Whipple (1929) reported that at least 8 of 10 carriers who underwent cholecystectomy were cured. Browning et al (1933) summarised the findings of a number of workers and showed that cholecystectomy alone cured approximately 75% of chronic carriers. Vogelsang (1950) found much the same proportion of cases cured by

cholecystectomy alone, thus about 25% of carriers continued to excrete despite the removal of the gall bladder.

As early as 1907, Dehler drained the gall bladders and cystic ducts of two faecal carriers and succeeded in freeing the bile of organisms after a few weeks of drainage. Later he performed cholecystectomy combined with drainage of the hepatic duct (Dehler 1912), drainage being continued until the bile was free of organisms. Garbat (1922) also believed that free drainage of bile was a major factor in the clearance of the biliary carrier, and Schottmuller and Fraenkel stated clearly in 1925 that the infection could lie solely in the intrahepatic bile passages and was not always in the gall bladder itself. In 1960 Erlic and Reitler described 4 chronic carriers, all of whom suffered from biliary colic. Two patients had cholecyst-:ectomy performed with drainage of the common bile duct and deep irrigation with chloramphenicol or oxytetracycline solution. A third patient, who had cholecystectomy performed 6 years before she developed typhoid fever, had drainage and irrigation after removal of soft stones from the hepatic ducts. In all these cases bile culture was positive before and at operation but became negative 3 - 10 weeks after operation and remained so for 4 years after removal of the drainage tube. A fourth patient underwent

cholecystectomy alone and was not cured of the carrier state.

These findings suggest that while cholecystectomy alone will cure carriers if the chronic infection is localised to the gall-bladder, there are other intrahepatic carriers in whom drainage and irrigation of the deep bile passages is required. In the same way some urinary carriers, if only one kidney is affected, may be cured by nephrectomy, (Nichols et al.1919), but a few continue to excrete.

While it is possible therefore to cure most carriers by surgical means, some patients may refuse operation and others be unfit for it. It is still desirable to find a cure which does not involve surgery.

(iii) Classification of Carriers.

One classification of carriers is based on the duration of excretion. Carriers who clear themselves within a year after the acute illness are called temporary, while persons who excrete for longer than that are considered to be unlikely to clear themselves and are called chronic carriers (Ledingham and Arkwright 1912).

Carriers have also been classified according to possible sites of persistent infection, although not all of these sites

have been proved by demonstration of the organism (Vogelsang 1950). Those sites may be:-

(i) Where the bacilli are discharged via faeces, from

(a) Intestine

(b) Gall Bladder

(c) Liver or bile ducts

(d) Pancreas

(ii) Where the bacilli are discharged via urine, from

(a) Parenchyma or pelvis of kidney

(b) Bladder

(iii) Where the bacilli are discharged from other sites

(a) Genital tract

(b) Through sinuses from bone and other sites

(i) (a) Intestinal carriers

It has been suggested (Garbat 1922, Saphir et al 1942) that in cases in whom no organisms are found on repeated duodenal intubation the focus of chronic infection is in the intestinal canal. The organism may exist there as part of the normal bowel flora, as seems likely in symptomless excreters, or there may be a focus of infection within the Peyer's patches as there is in acute typhoid fever. Vosburg and Perkins (1925) found S. typhi in the appendices of 4 out of 7 chronic carriers when they

performed cholecystectomy and claimed that these patients would not have been cured of their carrier state without appendicectomy. The number of intestinal carriers reported is, however, small, and none has been confirmed pathologically.

(i) (b) Gall Bladder Carriers

It has been recognised that typhoid carriers may be cured by cholecystectomy. In these cases it is common to find gall-stones, most of which contain typhoid bacilli (Vogelsang 1950). The gall-bladder wall, however, usually shows either no histological changes or only those of non-specific chronic cholecystitis, although Browning and his co-workers observed localised collections of plasma cells and lymphocytes, resembling lymphoid nodules, in the muscosa (Browning etal.1933). It seems more likely that the infection comes to rest in and may aggravate an already inflamed stone-containing gall-bladder rather than that the stones are produced solely as a result of typhoidal infection. Vogelsang (1950) grew S. typhi from the contents, other than stones, of 53 out of 54 gall bladders removed from carriers, but he too found only mild inflammatory changes in the gall bladder walls. Thus although the bile was heavily infected the gall bladder itself was not specifically involved.

(1) (c) Liver and Bile Duct Carriers

About a quarter of the typhoid carriers who undergo cholecystectomy continue to excrete S. typhi. The infection may be present in the bile ducts: for example, Erlik and Reitler (1960) reported a case of a woman who had undergone cholecystectomy 6 years before an attack of typhoid fever, but who developed symptoms of obstructive jaundice and cholangitis 5 years after recovery from the acute illness and was then discovered to be a faecal carrier. At operation she was found to have many soft calculi in the hepatic and common bile ducts and these concretions gave a profuse growth of S. typhi. After 10 weeks of drainage and irrigation of the deep bile passages with oxytetracycline bile culture remained negative.

It is known that the liver is a site of proliferation of bacteria during the course of acute typhoid fever and that sometimes small areas of intralobular necrosis may result (Gaffky 1884). Normally when the acute infection subsides the liver, as with other tissues, is cleared of infection and the damaged tissue restored to normal. However it is possible that granulomata or microscopic foci of infection may persist, particularly if there is some obstruction to free flow of bile at the time of the acute illness. Bersch (1926) grew S. typhi from small portions of

liver excised from a carrier at the time of cholecystectomy although his findings could not be confirmed by Browning et al. (1933).

(i) (d) Pancreatic Carriers

The pancreas may be inflamed in acute typhoid fever (Deaver and Pfeiffer 1914) and the pancreas as a site of chronic infection was suggested by Moynihan in 1903. Vogelsang (1950) described 2 typhoid carriers from whom a sterile gall-bladder was removed and bile culture was negative. However the duodenal fluid in both cases was highly infected and remained so after operation, and both cases continued to excrete S. typhi in faeces. Sawyer (1915) recorded a similar case. Vogelsang suggested that in these instances it was possible that the infection entered the duodenum below the bile passages through the pancreatic duct, although this was never proved.

(ii)(a) Urinary Carriers

Most urinary carriers show pathological changes in the urinary tract, commonly parenchymal abscess formation or

pyonephrosis with or without secondary pyelitis or cystitis (Bumke 1925). Browning et al.(1933) quoted a case of Steinthal's of a urinary carrier who was cured by removal of one kidney and ureter. When these were examined both were found to be healthy but S. typhi were cultured from the pelvis of the kidney. However this finding appears to be unusual. Urinary carriers are frequently found to excrete only intermittently, in much the same way as a patient with chronic pyelonephritis has intermittent acute attacks. As with gall-bladder infections it is difficult to determine whether typhoid bacilli persist in a previously damaged or obstructed urinary tract or whether they are the cause of the damage.

(ii) (b) Bladder Carriers

It is unusual to find bladder infection without a focus higher up the urinary tract, although Garbat (1922) reported one such case.

(iii) (a) Genital Tract Carriers

Although no local pathology in the genital tract has

been demonstrated in typhoid carriers S. typhi may be obtained by high vaginal swab during acute typhoid fever. Brodie and Davidson (1944) found that a vaginal swab taken from a paratyphoid carrier gave a positive culture on 2 occasions. Faeces and urine culture taken at the same time were negative and on the second occasion had been so for several weeks.

(iii) (b) Typhoid infections of bone

It is not rare to find a chronic focus of infection in bone, in particular in the long bones or ribs (Browning et al 1933). Such cases may present as acute local swellings or may resultnin slow sinus formation. For example, a woman in Aberdeenshire in 1939, who had had typhoid fever 23 years earlier, presented with a sinus from a focus in rib.

Other sites of chronic infection have been reported, for example tonsils (Bumke 1925), but these are rare.

B. The Site of Chronic Infection

Whereas many carriers have gross pathology to account

for a chronic focus of infection, for example gall stones or pyonephrosis, there are some types of carrier in whom the nidus of infection has not yet been satisfactorily located. Such typhoid carriers are usually healthy. There are two possible explanations of this absence of localising symptomatology:-

(a) that there is one central focus of infection which produces no obvious pathological changes but which causes frequent re-infection of bile and perhaps of blood. Browning et al (1933) considered that contamination could not always be blamed for the occasional positive urine specimen obtained from some faecal carriers, and suggested that transient bacteraemia with localisation in the kidney was a possible cause. They quoted Ebeling's case of a suspected healthy carrier of many years' duration who was found on one occasion to have bacteraemia (see page 187). Goebbel (1914) performed necropsies on 2 typhoid carriers: in addition to the expected finding of bacilli in gall-bladders and bile ducts he isolated them from spleen and liver.

(b) That there are several sites in the body where bacteria may remain after the end of the acute illness without causing

gross pathological changes. From these sites they are released only locally, for example from Peyer's patches into intestine or from pancreas into duodenum.

Whatever the organ or organs involved in the persistence of bacteria in the carrier state, it seems very probable that such bacteria may survive in the tissues without producing the active lesions which usually characterise their relationship with a host. This different relationship may be due to a variation in either the pathogen, the host environment, or both. When the aetiology of relapse was discussed it was suggested that the intracellular bacteria which persist may be in a state of growth analogous to the lag phase of the bacterial growth cycle and that on reversion to the logarithmic or active phase they multiply sufficiently to cause a relapse. Hopps et al (1961) suggested that there may be also a drug-induced slow rate of growth of bacteria resulting in their multiplication, for example, only every week instead of every 30 minutes. It seems eminently possible that there may exist, without the influence of drugs, a form of bacterium which is either in a prolonged "lag" phase or has a very slow rate of growth.

McDermott (1958) believed that microbial persistence is due in part at least to the "adaptive plasticity" of the organism. He suggested that a bacterium may survive in the face of antibiotic therapy because its form is altered. Weibull (1955) showed that when the cell wall of a bacterium is destroyed under certain conditions the bacterial cytoplasm and its limiting membrane may continue to exist as "protoplast". Without a rigid cell wall the protoplast is smaller, soft, and easily distorted. McDermott believed that protoplast is the origin of L - forms of bacteria and of pleuro-pneumonia-like organisms (PPLO), and suggested that it is analogous to the drug-induced spheroplast form of a bacterium. Protoplast forms need not necessarily be drug-induced, however. Pease (1965) observed that many bacteria produce their L-forms without interference. She also pointed out that the loss of the cell wall can reduce the pathogenicity of bacteria because of the absence of certain antigenic components. Such a bacterial form could well persist in a state of balance with a host so that neither was obviously damaged by the other and both survived.

It is probable that environment factors also play a part in microbial persistence. Although no absolute proof has yet been obtained that S. typhi exists intracellularly in the carrier

state the concensus of opinion is that this is the case. It was stated earlier that S. typhi is a facultative intracellular parasite i.e. it is capable of adapting its nutritional requirements so that it may survive intracellularly. The intracellular position both protects the pathogen from the action of humoral defence mechanisms such as antibody and also prevents its continued stimulation of these immune responses. This would be an additional explanation of the absence of obvious tissue reaction in some carriers.

If the bacterium is intracellular the host cell may be unhealthy or inefficient. Showacre et al (1961) observed that drug-induced spheroplast formation did not seem to occur in healthy tissue culture cells but was evident in dead or dying cells. They did however observe occasional living healthy cells which contained spheroplasts and suggested that these may have been ingested by phagocytosis after being formed extracellularly or in a dying cell.

Protoplasts are capable of prolonged inactivity in a suitable environment which may be intracellular. Wittler et al (1956) observed that PPLO forms of corynebacterium

showed little or no cytotoxicity for the cells in which they were situated until yeast extract was added to the extracellular fluid. Following this there was extensive tissue destruction by the organisms. This demonstrated clearly that a change in the environment could alter the activity of the PPLO forms.

Thus it may be seen that under certain conditions some forms of bacteria are capable of surviving intracellularly for prolonged periods in a state of equilibrium with their host. There is no reason to believe that this situation does not obtain in the chronic typhoid carrier. The effect which antibiotic drugs may or may not have on such organisms is at present the subject of further research in Aberdeen and will not be discussed in this thesis.

It is not known which type of tissue cell, if any, acts as host in the carrier state. During the acute illness bacteria are ingested by the phagocytic cells of the blood and reticulo-endothelial system, and it is feasible that these same cells are involved in chronic typhoid infections. The bacteria may then be found in, for example, the Kupffer cells of the liver, the

sinusoidal epithelium in the spleen, and perhaps plasma cells in intestinal lymphoid tissues. On the other hand it is possible that if bacteria can live in reticulo-endothelial cells they can also survive in other tissue cells, once inside them. During the acute illness bacteria pass through liver cells on the way from blood to bile, and it is conceivable that an occasional organism remains there and multiplies sufficiently to produce the carrier state. Such a situation would allow frequent re-excretion into bile and occasional re-infection of the blood stream. It would appear that those faecal carriers who are not cured by cholecystectomy alone respond to cholecystectomy plus prolonged drainage and irrigation of the deep bile passages (Erlick and Reitler 1960). This points to the liver as the persistent focus of infection in such cases.

If the bacteria are intracellular, how are they released to be excreted? Wilson (1953) demonstrated that phagocytic cells containing bacteria could extrude some of them and remain viable. Smadel (1963) observed that this phenomenon was not uncommon in S. typhi tissue cultures, but that the cell never emptied itself completely of bacteria. It is tempting to suggest that bacteria within the cell are in an inactive form but are egested when they

change to an active rapidly growing form. In this way they would produce sufficient numbers outside the cell to be demonstrable in bile and excreta. This frequent reinvasion of bile by bacteria is compatible with the intermittency of excretion which is sometimes observed, and also with the presence of large numbers of extracellular bacteria which produce no systemic reaction.

Another possibility is that intracellular bacteria are released only when the host cell dies and disintegrates. The exact lifespan of phagocytic or of liver cells is uncertain, but the latter may survive for a period of years. This has been given as a possible explanation for the fact that in those typhoid carriers who have been cured by antibiotic therapy a very lengthy period of treatment has been necessary (Anderson, 1964). Whichever may be the method of release of bacteria, it seems unlikely that the number of bacteria small enough to reside intracellularly without causing tissue damage could produce the large number which are excreted unless the bacteria enter a rapid growth phase either just before or just after they become extracellular.

All these hypotheses about the nature and site of bacte ia in a chronic typhoid infection which shows no obvious pathology have still to be proved, or disproved, in man. If however the premise is accepted that such bacteria may be intracellular and in a form which is insensitive to presently known natural or chemotherapeutic bacteriocides, it is possible that some method of converting these bacteria to their more usual form will succeed in exposing them to elimination and the carrier state may then by cured.

C. A clinical trial of ampicillin in convalescent excreters.

When Christie (1964) reported that 7 of 8 chronic carriers had ceased to excrete for at least a year after a three months' course of ampicillin, it was felt that the answer to the problem of the chronic carrier might have been found. The action of ampicillin in chronic carriers is not fully understood; while it reaches a high concentration in bile, inflammatory fluid and lymph (Broom 1964) it shows only moderate intracellular penetration (Bramfitt 1964). It has been suggested however that the success of prolonged treatment lies in the fact that as the cells, 3 containing the organisms die and are shed, the bacilli which

are released are killed by ampicillin (T. Anderson 1964, Stewart 1964). Certainly Bullock (1963) found that only 3 of 7 carriers remained negative after 12 - 21 days of ampicillin therapy, whereas Troy (1964) and Whitby (1964) achieved success in the treatment of small numbers of chronic carriers with ampicillin in doses of 4 - 5 G. daily for 4 - 6 weeks. It is not yet known how long treatment on this basis should be continued since the life span of reticulo-endothelial and liver cells is uncertain.

When typhoid fever occurred in Aberdeen it was considered useful to test the efficacy of ampicillin in preventing the chronic carrier state rather than curing it. With a possible 507 cases of typhoid, about 160 temporary and 16 chronic carriers might be expected. It was decided therefore to conduct a double-blind trial of ampicillin in early convalescent excreters, using a strictly random allocation of identical ampicillin and inert capsules. The term 'convalescent excreter' was used firstly to distinguish early excreters from patients who still excreted after the period of convalescence i.e. about a month from the end of illness, and secondly to avoid the use of the word "carrier" in the presence of the patients. It was not thought that there would be a sufficient number of patients to test more than one drug or one duration of treatment. In view of the extent

of the publicity which attended this outbreak and the treatment of the patients, it was considered necessary to explain fully to the patients the conduct of and reason for the trial and to invite them to participate. It was also agreed to carry out a sequential analysis of the results so that if ampicillin were clearly of value the trial would be stopped and all excreters treated with it. In the event, sequential analysis gave no clean result. The trial was conducted by Dr. W. Walker, Dr. A. Sutherland and the author, and statistical advice was given by Dr. S.J. Kilpatrick of the Department of Public Health and Social Medicine, University of Aberdeen. All specimens of faeces and urine were examined at the laboratory, City Hospital, Aberdeen. Beechams Limited kindly provided 3000 of the 8000 capsules of ampicillin which were used and all the inert capsules.

(i) The Conduct of the Trial

The trial was timed as early in convalescence as was feasible, since most patients were feeling well and anxious to return home. The agreed criteria for discharge from hospital were three negative specimens of both stool and urine at 4 day intervals commencing 4 days after the end of the initial illness. It was therefore

decided that any positive specimen occurring during this period would make the patient eligible to enter the trial provided certain additional criteria were fulfilled. These were:-

1. No known penicillin sensitivity.
2. No other antibiotic therapy at that time.
3. Consent of the patient after having the double-blind nature of the trial, and its purpose, fully explained.

The dosage of ampicillin was 1 G. 6 hourly for adults, 0.75 G. 6 hourly for children age 6 - 12 years and 0.50 G. 6 hourly for children under 6 years. Both ampicillin and inert capsules were given for 10 days, a longer course of treatment not being feasible because of possible lack of co-operation. Patients entering the trial were allocated to one of the two groups by a strictly random method. The key to the allocation was held by the medical staff of the Typhoid Co-ordinating Centre, to whom physicians in clinical charge of patients could apply in case of need.

There were three agreed reasons for withdrawal from the trial:-

1. Sensitivity reaction to ampicillin.
2. Clinical relapse of typhoid fever.
3. The administration of another antibiotic for any reason.

"Success" was judged to be the absence of the organism in all specimens of stool and urine taken after the trial had been completed. Three paired specimens (stool and urine each time) were taken at 4 - day intervals in hospital starting 4 days after "treatment" ceased; if these were all negative the patient was discharged from hospital and a minimum of another three paired specimens were collected at weekly intervals at home. A further three sets of specimens were to be tested at 3, 6, 12 and 24 months after discharge, the faeces specimen to be taken after a saline purge was given. Failure was judged to be the re-appearance of the organism in any one specimen at anyntime after the trial treatment period.

(ii) The Analysis of the Trial

Of 114 patients who entered the trial 23 were withdrawn, 1 because of penicillin sensitivity and 22 because of clinical relapse. A further 6 patients relapsed immediately on completing the trial. The results were therefore assessed on 85 patients, as is shown in Table 39 (i). There were fewer "failures" who had ampicillin, the difference being of borderline significance ($x^2 = 3.99$ $p < 0.050$). Since it might be argued that the six patients who relapsed after completing the trial were "failures"

TABLE 39

THE ASSESSMENT OF THE RESULTS OF THE CLINICAL TRIAL OF AMPICILLIN

(1) THE RESULT ASSESSED ON 85 CONVALESCENT EXCRETERS

TREATMENT	SUCCESS	FAILURE	TOTALS
AMPICILLIN	35 (30)	10 (15)	45
CONTROL	22 (27)	18 (13)	40
BOTH TREATMENTS	57	28	85

$\chi^2 = 3.99$ D.F. = 1, $P < 0.05$

POSSIBLY SIGNIFICANT.

(2) THE RESULT ASSESSED ON 85 CONVALESCENT EXCRETERS PLUS 6 PATIENTS WHO RELAPSED AFTER COMPLETING THE TRIAL

TREATMENT	SUCCESS	FAILURE	TOTALS
AMPICILLIN	35 (29)	11 (17)	46
CONTROL	22 (28)	23 (17)	45
BOTH TREATMENTS	57	34	91

$\chi^2 = 6.06$ D.F. = 1, $P < 0.0250$

POSSIBLY SIGNIFICANT

the assessment was repeated with the inclusion of these patients (Table 39 (ii)). This result was of possible significance in favour of ampicillin ($x^2 = 6.06$ $p < 0.0250$). However the patients who relapsed had not reached the end of the acute illness when they participated in the trial and therefore were not true convalescent excreters, if convalescence is considered to begin only after the end of the complete illness and not merely after the initial illness.

From these results it is not possible to say more than that ampicillin given to early convalescent typhoid excreters may have some effect in preventing the persistence of excretion. Further trials of ampicillin at this stage of the illness would be justified and of value.

The age and sex distributions of the 85 patients in the trial are shown in Table 40, not significantly different from those of other convalescent excreters. The two trial groups, "successes" and "failures", were compared on the basis of age, sex, severity of the initial infection and daily dosage of ampicillin but no differences were found. The effect of different treatments for the initial illness on patients in the trial was then considered.

TABLE 40

AGE DISTRIBUTION OF CLINICAL TRIAL PATIENTS COMPARED WITH ALL TYPHOID FEVER PATIENTS AND ALL CONVALESCENT EXCRETERS

AGE GROUP (YEARS)	NUMBER OF:		
	TYPHOID FEVER PATIENTS	CONVALESCENT EXCRETERS	CLINICAL TRIAL PATIENTS
0 - 14	108 (.2)	50 (.3)	37 (.45)
15 - 29	126 (.3)	41 (.3)	19 (.2)
30 - 44	75 (.2)	25 (.2)	10 (.1)
45 - 59	86 (.2)	25 (.2)	15 (.2)
60 & OVER	74 (.2)	18 (.1)	4 (.05)
ALL AGES:	469 (1.0)	159 (1.0)	85 (1.0)

390 patients had been given a course of chloramphenicol and the remainder had been treated with ampicillin or a mixture of drugs, usually ampicillin and chloramphenicol. This meant that patients in this minority treatment group who received ampicillin in the trial were, in fact, having a second course of ampicillin. However there was no significant difference between the two trial groups in numbers of patients who had received chloramphenicol, ampicillin or other initial treatment, nor did these different treatments have any significant effect on the results of the trial when the two groups were assessed apparately.

CONCLUSION:-

A clinical trial of ampicillin in 85 convalescent excreters did not clearly establish the value of ampicillin in reducing the incidence of temporary carriers. However the result was not unfavourable, the timing of the trial was not ideal, as is illustrated by the number of patients who relapsed during or after participation in the trial. In these cases the positive isolation which rendered the patient eligible for the trial occurred during the acute stage of the illness and not, strictly, in convalescence. It points the need for a further controlled trial of ampicillin a few weeks later in

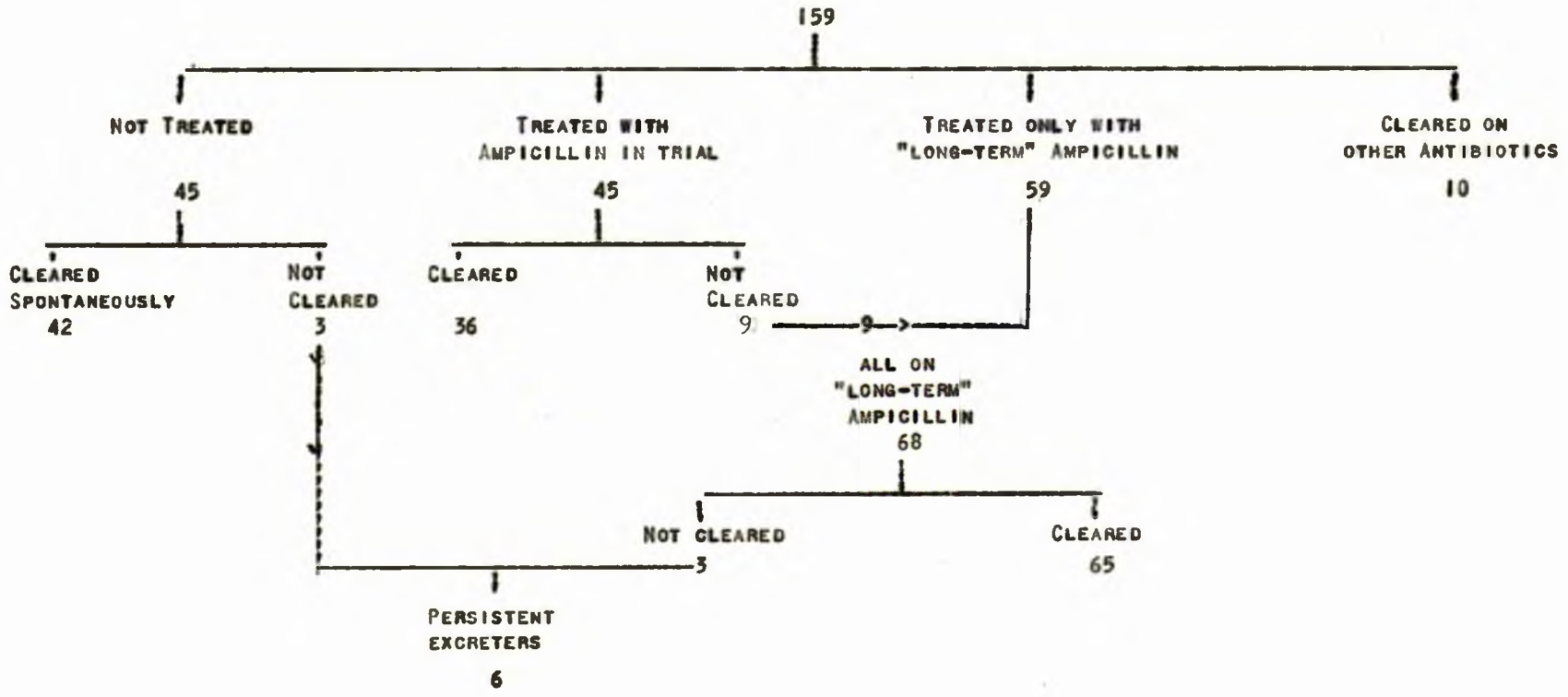
convalescence, with varying dosages and durations of treatment.

C. Further treatment of Convalescent Excreters

(i) Prolonged treatment with ampicillin

There were 159 convalescent excreters in Aberdeen; their treatment and outcome are shown in Figure 18. By the middle of July 1964, i.e. 2 months after the beginning of the outbreak, some of them had cleared spontaneously, some had become negative while on ampicillin in the trial and others had become negative during treatment with ampicillin for other reasons. There were still, however, a number of patients excreting S. typhi who were being detained in hospital for this reason. The final assessment of the trial of ampicillin had not yet been made, but the majority of clinicians believed it to be of value and, therefore, although a second trial was scientifically desirable it might have been unethical and was, in the circumstances, certainly impracticable. All these patients therefore, unless they were known to be allergic to penicillin were started on a three month course of ampicillin in a dosage of 1 G. 8-hourly for adults and 0.75 G. 8-hourly for children. This rendered the excreta of almost all patients negative and they were discharged from hospital under the accepted

FIGURE 18. THE TREATMENT AND OUTCOME OF 159 CONVALESCENT EXCRETERS



clearance regime for discharge of 3 paired negative specimens of faeces and urine at 4 day intervals. Weekly specimens of faeces and urine were collected from all these patients while they were on ampicillin and "clearance" for them after the end of treatment was as for the other patients i.e. 3, 6 or 9 paired negative specimens at weekly intervals and each following a saline purge. (see page 65).

There were 78 of the 469 cases (16.6%) who continued to excrete for more than a month after the end of the acute illness, a figure comparable to that found by Garbat (1922). Of these 78, 10 were not given "long-term" ampicillin, 5 because of known penicillin sensitivity and 5 because they were very reluctant to be treated and were given a further chance to clear themselves spontaneously, which they did. A further 16 patients did not complete the course of treatment, 10 because of sensitivity reactions, 3 because of diarrhoea and 3 because of apathy. All 16 remained negative thereafter.

(C). (ii) Other Treatment of Convalescent Excreters

Methacycline 300 mgs. 6 - or 8 - hourly was used to treat 7 convalescent excreters, all of whom had produced several positive faecal specimens before starting this treatment. Three of them

became negative and remained so, and one had a single positive isolation after treatment but became negative thereafter. The remaining three became chronic carriers. However in most cases this antibiotic which reaches high concentrations in bile, rendered stool specimens negative during treatment which cephaloridine, for example, did not.

Of the 52 patients who completed the 3 months course of ampicillin 3 continued to be temporary carriers. In addition 3 penicillin-sensitive patients also continued to excrete. These 6 persistent excreters will be discussed more fully later in this chapter.

This relatively low incidence of possible chronic carriers, at 1%, may have been a feature of the particular strain of S. typhi which caused this outbreak, as it was at Oswestry (Jones 1951). However the incidence of convalescent excreters up until a month after the end of the acute illness was much the same as is usually observed. It is possible that the treatment of convalescent excreters with ampicillin, whether for 10 days or for 3 months, did have an effect in reducing the incidence of chronic carriers.

Convalescent Excreters in Aberdeen

The age distribution of the 159 patients who excreted during convalescence is shown in Table 40. There were just significantly more children in this group than expected ($x^2 = 9.68$ $p < 0.05$). The excess of children was discussed earlier when "post-treatment pyrexia" was examined (see page 134). The sex distribution of these and other patients was not significantly different, nor was the incidence of relapse. It was stated earlier that significantly fewer inoculated than uninoculated adults became convalescent excreters ($x^2 = 9.98$ $p < 0.005$), and also that patients who had a mild initial infection were very significantly less likely to excrete during convalescence ($x^2 = 15.33$ $p < 0.0005$). However, when the effect of the severity of the initial infection on convalescent excretion was examined in age groups, it was found to be possibly significant only in patients aged 60 and over ($x^2 = 5.21$ $p < 0.05$), although the same trend was evident in all age groups. This difference in the 60 and over age groups was caused by the large number of uninoculated excreters in this group.

There was no significant difference in the schedule of chloramphenicol treatment received initially by convalescent excreters and other patients. In excreters treatment started on

SECTION VII

TABLE 41

COMPARISON OF 159 CONVALESCENT EXCRETERS WITH OTHER TYPHOID PATIENTS

FACTOR	CASES COMPARED	SIGNIFICANT DIFFERENCE PRESENT
1. SEX DISTRIBUTION	ALL OTHER CASES	NO
2. AGE DISTRIBUTION		YES
3. INCIDENCE OF RELAPSE		NO
4. NUMBER OF INOCULATED ADULTS	ALL OTHER ADULTS	YES
5. SEVERITY OF INITIAL ILLNESS	ALL OTHER PROVED CASES	YES
(A)		
(B) IN AGE GROUPS 0-14	ALL OTHER PROVED CASES IN THE SAME AGE GROUPS	NO
15-29		NO
30-44		NO
45-59		NO
60+		YES
6. INITIAL TREATMENT		
(A) TYPE OF TREATMENT	ALL OTHER TREATED CASES	NO
(B) CHLORAMPHENICOL		
DAYS OF ILLNESS BEFORE TREATMENT	ALL OTHER CASES	NO
DAILY DOSE		NO
DURATION	TREATED WITH CHLORAMPHENICOL	NO
DURATION OF PYREXIA ON TREATMENT - 'MODERATE' CASES		NO
'SEVERE' CASES		NO

average, at 7.1 days of illness and continued for 14.1 days in a daily dose of 30.0 mg. per kg. bodyweight, the temperature becoming normal after 4.2 days.

In other patients treatment commenced, on average, after 7.8 days of illness and was continued for 13.9 days in a mean daily dose of 29.0 mg. per kg. body weight, the temperature becoming normal after 4.6 days.

There was no significant difference in the numbers of patients in each group who had chloramphenicol or other treatment initially.

Conclusions:-

It was found that children were more likely to become convalescent typhoid excreters but that for adults previous immunisation decreased the likelihood of excretion during convalescence. Patients who were severely ill on admission were also more likely to become convalescent excreters.

Natural Clearance Rate during Convalescence

There were 42 convalescent excreters who cleared themselves

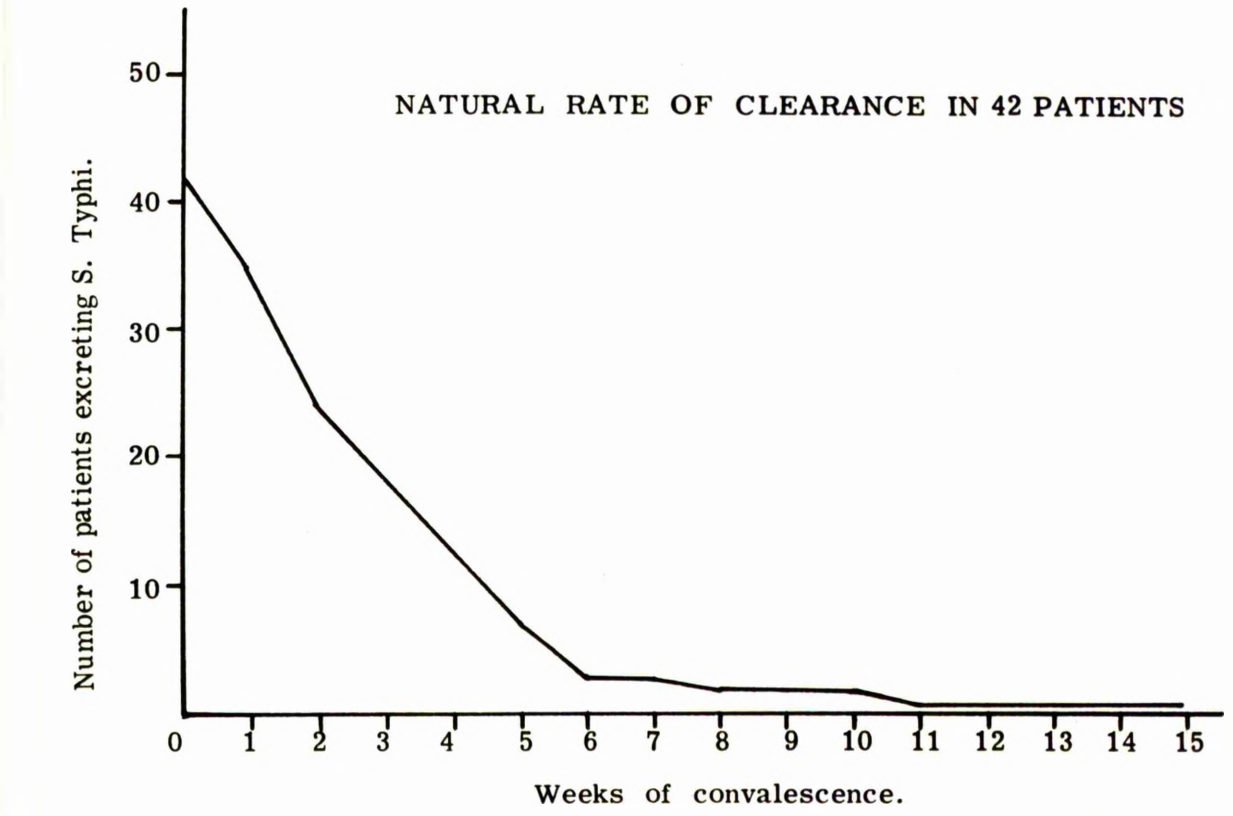


Fig. 19 - Natural Rate of Clearance in 42 Patients.

without treatment. The duration of illness at the time of the last positive specimen in these patients was known and it was therefore possible to assess the rate of natural clearance in this outbreak. (see Figure 19). An attempt was then made to compare this rate with the rate of clearance of patients who were treated with ampicillin. However the two groups of patients were dissimilar, since those patients who were permitted to clear spontaneously were, in the main, allergic to penicillin and furthermore the timing and duration of ampicillin therapy varied considerable. Comparison of the rates of clearance was therefore not valid.

(E) Chronic Typhoid Carriers in Aberdeen

(i) A description of the chronic carriers in Aberdeen.

There were 6 patients in Aberdeen who continued to excrete S. typhi for longer than 6 months; 5 at least of these have become chronic carriers. (1). The details of the laboratory findings in these 6 patients are shown in appendix VII 4.

Patient No. 531, a woman of 46, was admitted on the

TABLE 42

DETAILS OF THE SIX TYPHOID CARRIERS IN THE OUTBREAK OF TYPHOID FEVER IN ABERDEEN IN 1964

No.	SEX	AGE	INCUBATION PERIOD (DAYS)	SEVERITY	DAYS OF ILLNESS BEFORE TREATMENT	DOSAGE OF CHLOR-AMPHENICOL MG/KG.	DURATION OF CHLOR-AMPHENICOL (DAYS)	DAYS OF PYREXIA ON CHLOR-AMPHENICOL
72	F	34	10	2 → 3	9	23	14	4
531	F	46	12	3	27	28	14	5
113	M	53	7	3	8	29	16	9
48	F	62	?	2 → 3	9	27	14	5
291	F	67	24	3	7	19	16	8
524	M	70	6	2 → 3	12	29	14	3

27th day of illness because of breathlessness. She was found to have had a pulmonary embolus following a deep venous thrombosis of leg after a prolonged influenzal type of illness at home. On admission, Widal's reaction showed only S. typhi 'H' antibodies at 1:320 dilution, and a faeces specimen was positive 3 days later although urine and blood cultures were negative. Her incubation period was 12 days. Her temperature became normal on the 5th day of a course of chloramphenicol lasting for 14 days, to a total dose of 35 G. combined with anticoagulant therapy. However, specimens of faeces remained positive while she was participating in the trial (control group) and she then had 10 days' treatment with ampicillin 1 G. 6-hourly. During this course one serum ampicillin level at 4 hours was 0.96 µg. per ml. After 3 negative specimens she again excreted S. typhi and was given a 3 month course of ampicillin 1 G. 8-hourly. Faeces culture was negative until the last week of tr atment, when it again became positive. A further 5 week course of ampicillin 1 G. 8-hourly with methacycline 300 mg. 8-hourly was given. Once again she gave negative specimens during treatment but became positive as soon as treatment stopped. A month later a second three month course of ampicillin 1 G. 8-hourly, this time with probenecid 0.5 G 8-hourly. Serum ampicillin levels

ranged from 7.68 µg. per ml. at 2 hours to 1.92 µg. per ml. at 8 hours, the mean inhibitory concentration of ampicillin for S. typhi in serum being about 0.5 µg. per ml. Weekly specimens throughout were negative but 13 of 16 faeces specimens since have been positive. This woman is grossly overweight and has a long history of mild flatulent dyspepsia; her last severe attack was six years ago. Cholecystogram revealed only faint concentration of dye and a single laminated gall-stone.

Patient No. 113, a man aged 63 of stocky build, who was immunised with TAB vaccine in 1941-43, was admitted on the eighth day of illness with an incubation period of 7 days. Blood, faeces and urine culture were positive on admission and he had S. typhi 'H' agglutinins to 1:25 dilution. He became severely ill but his temperature fell to normal on the 9th day of a 16-day course of chloramphenicol, a total dose of 32 G. He had a positive faecesspecimen 5 days later followed by a further 6 at 4 day intervals, 3 while he was having inert capsules during the clinical trial, and 3 afterwards. A course of ampicillin 1 G. 8-hourly for

3 months was commenced; during this time he produced a positive faeces specimen after a month of treatment. All urine specimens were negative. At the end of treatment, weekly faecal isolations were immediately positive and remained so for five weeks. A further course of ampicillin 1 G. 8-hourly, plus methacycline 300 mg. 8-hourly, was therefore given for five weeks and this rendered his stools negative, but excretion recommenced as soon as treatment stopped. A month later he was given a further course of ampicillin 1 G. and probenecid 0.5 G. 8-hourly for three months, but faeces specimens remained intermittently positive on treatment and have been consistently positive since treatment stopped. Serum ampicillin levels with probenecid reached a maximum of 15.36 µg. per ml. at 2 hours and fell to 0.48 µg. per ml. at 8 hours. This man has a history, for 20 years, of mild flatulent dyspepsia aggravated by fatty foods, but cholecystogram revealed moderate concentration of dye by the gall-bladder.

Patient No. 48, an obese woman of 62, was admitted to hospital on the 9th day of illness with no history of exposure to infection but with symptoms suggestive of typhoid fever. *S. typhi* 'H' serum agglutination was present at 1:100 dilution

and clot culture, reported after admission, was positive. She was moderately ill but her temperature fell to normal on the 5th day of treatment with chloramphenicol which was continued for 14 days, to a total dose of 26.5 G. Five days later faeces culture grew S. typhi which were resistant to chloramphenicol and 4 days after that she relapsed, when a blood culture was positive for S. typhi sensitive to chloramphenicol, but stool culture again showed resistant organisms. She was severely ill on relapse but her temperature became normal on the third day of re-treatment with chloramphenicol which was again given for 14 days, to a total dose of 17 G. A faeces specimen was again positive 5 days after the end of treatment, and once more resistant to chloramphenicol. She had 10 days' treatment with ampicillin as part of the clinical trial, on the 4th day of which she developed acute cholecystitis which settled slowly over the next 6 days. She had another positive faeces specimen 15 days later, this time sensitive to chloramphenicol, and was therefore started on a three months' course of ampicillin 1 G. 8-hourly. Serum ampicillin levels at this time varied from 7.68 µg. per ml. 2 hours after oral administration to 0.48 µg. per ml.

at 8 hours. Weekly paired specimens of faeces and urine throughout were negative, as were 6 further weekly specimens after the course of ampicillin was completed. However, three months later the second of three weekly follow-up specimens taken after a saline purge was positive for S. typhi, and since then she has excreted first intermittently then continuously for 7 months, specimens being taken weekly. Cholecystogram showed "no definite evidence of a functioning gall-bladder" and possibly one gall-stone. This patient had no history of flatulent dyspepsia but had been taking a supposedly light diet for many years in an attempt to lose weight.

The fourth chronic carrier, patient no. 291, was a woman of 67 who was admitted on the 7th day of a severe illness. Her incubation period was 24 days. Blood, stool and urine cultures were positive but serum agglutination was negative. She responded slowly to treatment, her temperature becoming normal after 8 days of a 16-day course of chloramphenicol, total dose 23 G. She relapsed 12 days after the end of treatment and her temperature fell slowly over the first 8 days of a 14-day course of ampicillin 2 G. 6-hourly, total dose 112 G.

On the 10th day of ampicillin therapy she developed a marked generalised rash accompanied by quite severe diarrhoea. The rash responded only slightly to antihistamines. She had five negative paired specimens of faeces and urine in the next month but then 8 of the next 15 weekly faecal specimens were positive for S. typhi. During a six weeks' course of methacycline she gave no positive isolations but faeces once again became positive thereafter, and she was given cephaloridine 0.5 G. twice daily intramuscularly for one month. Serum cephaloridine levels ranged from 7.68 µg. per ml. at 2 hours to 0.12 µg. per ml. at 12 - 15 hours, the mean inhibitory concentration of cephaloridine for S. typhi being about 2 - 2.5 µg. per ml. Although the first 3 weekly specimens on this treatment were negative, only 4 of 38 subsequent weekly specimens have been negative. This woman is grossly overweight and has a history of mild dyspepsia for many years. Cholecystogram was unsatisfactory because of her obesity. The report stated that "there does appear to be concentration but it is difficult to exclude the presence of stones".

Patient No. 524, an overweight man of 70 who had been immunised with TAB vaccine in 1914-16, was admitted on the 12th

day of a moderate illness after an incubation period of 6 days. Blood, stool and urine specimens were negative and he had S. typhi 'H' agglutinins only to 1:50 dilution. His temperature became normal on the 3rd day of a 14 day's course of chloramphenicol, to a total dose of 25.5 G., but faec s specimens became positive after treatment and remained so. He was known to be allergic to penicillin and therefore was given a further course of chloramphenicol 3 weeks later for 11 days, to a total dose of 15 G. At this time he developed a phlebitis of his right calf although he was not confined to bed. Specimens of faec s remained positive throughout treatment and thereafter, and so a course of methacycline was started a month later but stopped after 4 days because of a marked sensitivity reaction. Subsequently he had 12 positive isolations out of 15. Three months later he was given tetracycline 1 G. daily for 6 weeks which he tolerated, rather surprisingly, and during this time all specimens were negative. However, excretion recommenced three weeks after this treatment and he was then given cephaloridine 0.5 G. twice daily intramuscularly for 1 month. Serum cephaloridine levels ranged from 7.68 µg. per ml. at 2 hours to

0.06 µg. per ml. at 12 - 15 hours. An occasional negative specimen was obtained during this time but 15 weekly specimens have been positive since. This man had no history of gastro-intestinal upset and cholecystogram revealed a normally functioning gall-bladder with no gall-stones.

These five patients have all become chronic faecal carriers. There is one further patient who may or may not have become clear of infection exactly a year from the time she became ill. This patient, No. 72, is a plump woman of 34; she was admitted on the 9th day of a moderate illness after an incubation period of 10 days. Blood and urine were negative but stool culture was positive and she had S. typhi 'H' agglutinins to 1:100 dilution. Her gall bladder was palpable and tender on admission. Her temperature became normal on the 4th day of treatment with chloramphenicol which was continued for 14 days to a total dose of 23 G. Faecal specimens were positive throughout this treatment and urine culture was also positive after treatment; she was therefore admitted to the trial and given ampicillin 1 G. 6 - hourly. However, on the 3rd day of this, i.e. the 10th day after the end of chloramphenicol and the 33rd day of illness, she relapsed suddenly and severely; at the same time

she developed a gross generalised sensitivity rash, thought to be caused by ampicillin. Treatment was changed to chloramphenicol and this was continued for 14 days to a total dose of 18 G; the temperature fell slowly, reaching normal on the second last day of chloramphenicol therapy. However, faeces and urine cultures remained positive. Ampicillin was tried again, but after two doses she was sick and feverish and a generalised rash appeared some hours later. Methacycline 300 mg. 6-hourly was given for 10 days; it rendered specimens negative during treatment but excretion began again immediately treatment stopped. For the next three months weekly faecal specimens were consistently positive and 8 urine specimens out of 12 were positive. A second course of methacycline, 600 mg. 8-hourly, was given for 5 weeks during which all specimens were negative. Since then she has had only one isolated positive urine culture, and this may have been contamination; however, weekly faeces culture was positive three weeks after stopping methacycline and she was given one month of cephaloridine 0.5 G. twice daily intramuscularly. Serum cephaloridine levels at this time ranged from 3.84 µg. per ml. at 2 hours to 0.015 µg. per ml. at 12 hours. Faeces specimens were positive throughout treatment and remained so for 10 weeks

thereafter, but since then this patient has given 28 negative weekly specimens and it is hoped that she may continue to do so; biliary culture has not yet been performed.

This patient had mild cholecystitis early in the acute illness, although she had no previous history of dyspepsia, and her cholecystogram showed a possible septum in a gall-bladder which was functioning normally with no evidence of stone formation. It is of interest that she volunteered the information, whatever it may signify, that since her specimens had become negative she had lost a feeling of epigastric fullness which she had experienced in the previous six months. It may be that a mild residual cholecystitis had cleared spontaneously thus permitting free flow of bile and perhaps removal of infected biliary calculi.

Antibody Levels of the Chronic Carriers

All 6 patients showed a normal response to infection, although only two, both men who had been immunised in the past, showed S. typhi 'O' antibodies, one at 3 months and one at 6 month follow-up. Vi agglutination, which is commonly thought to be an approximate index of the carrier state (Ministry of Health 1945) was no different in these patients from others on discharge

from hospital and certainly not as high as in some. In 3 of these patients the level of Vi agglutination fell after discharge to between nil and 1:10 dilution and in 2 it remained static at 1:10 or 1:20 dilution. The other patient, No.48, showed a rise in Vi titre from 1:80 on discharge to 1:320 at 6 month follow-up i.e. at the time she was again found to be excreting. Wilson and Miles (1965) state that although about 85% of chronic carriers show Vi agglutination in serum in titres of 1:5 or over, "the presence of Vi agglutinins is in no sense diagnostic of the carrier state nor does their absence exclude it. The findings in these 6 patients in Aberdeen would agree with this. If, as is believed, there are two types of chronic carrier, it is conceivable that in carriers in whom there is an active focus of chronic infection Vi agglutination is at high level, whereas if the bacteria are living a parasitic or saprophytic existence Vi agglutination is only slight or may well be absent.

Discussion

These 6 patients differ from other patients in the outbreak in several ways. As has been found by most previous observers

(Ledingham and Arkwright 1912) all are adults, the youngest being 34 years of age. All are overweight, in varying degrees, and 3 have a history of flatulent dyspepsia. It is not known how many other patients in the outbreak had a similar history, nor is the state of the gall-bladder known in other patients, but at least 4 of the carriers have diminished gall-bladder function. One man, however, has no history of dyspepsia and has a normally functioning gall-bladder, so that the incrimination of the gall-bladder does not necessarily apply to all these cases.

All 6 carriers had a severe illness and 3 of the women relapsed. Chloramphenicol therapy was not initiated in any before the 7th day, and the mean days of illness before treatment was 12.0 days as opposed to 6.3 in other patients. Treatment was given, on average, in a daily dose of 26.9 mg. per kg. bodyweight for 14.7 days, compared with 29 mg. per kg. for 13.9 days in other adults. The mean duration of pyrexia on treatment in carriers was 5.7 days compared with 5.2 days in other severely ill adults.

Three of these patients were treated for 3 - month periods with ampicillin. It may be argued that the dosage of ampicillin, at 1 G. 8-hourly, was inadequate, but serum ampicillin levels, when probenecid was not given were frequently much above the mean inhibitory concentration against S. typhi and only very slightly below, at the time that the next dose was due. It would appear either that more prolonged and higher dosage of ampicillin is required to clear bacteria from the tissues regardless of the serum levels at which ampicillin is active against S. typhi, or that this drug is not generally effective against the form of bacteria which persists in chronic carriers.

In 3 persistent excreters who were severly allergic to ampicillin other oral antibiotics, namely methacycline and tetracycline, were tried without success. Intramuscular cephaloridine was then given, but it too was unsuccessful in clearing these patients of infection; indeed it was less effective than methacycline in arresting the excretion of bacteria during the period of administration. The serum cephaloridine assays performed suggested that satisfactory serum concentrations were attained for at least the major part of each day, but again this may not reflect the active tissue concentration. It might be that, as with ampicillin, a longer course would have had more success.

CONCLUSIONS:-

Of the 6 possible chronic faecal carriers in Aberdeen 4 at least have some diminution of gall-bladder function, but this may not be the only cause of the chronic carrier state. All these patients had a severe illness which was treated later than in other patients. In the dosage and for the duration given ampicillin was not found to be effective in curing the carrier state.

SUMMARY AND CONCLUSIONS

In 1964 an outbreak of typhoid fever occurred in Aberdeen, Scotland. The infection was presumed to have spread from a 6 lb. can of corned beef in a supermarket. There were 469 proved cases and a further 37 in whom typhoid fever was strongly suspected. Infected food was bought over a period of 18 days. The outbreak took the shape of a single wave and there were no proved secondary cases. There were 3 typhoid deaths and 6 possible chronic carriers.

Admission of patients to hospital was controlled, where practicable, by awaiting the result of serological assays before admission, unless the organism had been isolated. This prevented the unnecessary admission of "panic" cases. Patients were discharged from hospital after 3 consecutive negative paired specimens of faeces and urine during convalescence, and further specimens were obtained at home to a maximum of 12 paired specimens in all from professional food-handlers. Further testing was planned at intervals over a period of 2 years.

The clinical features were, in the main, those of classical typhoid fever, but many early cases had profuse diarrhoea in the first week of illness. The severity of the initial illness was defined by height and duration of pyrexia. The severity of the overall illness was defined on the same basis except that cases of death, relapse or complication were rated as severe.

It was found (a) that patients with severe initial infection took longer to respond to treatment and were more likely to relapse or to become convalescent excreters, and (b) that previous immunisation greatly reduced the severity of the complete illness. A universally agreed definition of severity of illness is essential, however, before comparisons of the effect of prophylaxis and treatment are possible between different outbreaks.

Patients with complications other than relapse were, in general, older than other patients and responded more slowly to treatment of the initial illness.

Chloramphenicol was the main drug used in the acute illness but ampicillin was given to some children, and consecutive courses of ampicillin and chloramphenicol to others. Patients treated with ampicillin had a longer fever than those given chloramphenicol. However the relapse rate after ampicillin alone was nil, compared with 19% in patients given chloramphenicol alone. It is suggested that in patients who are not severely ill ampicillin might be given in an attempt to reduce the risk of relapse.

The pathogenesis of relapse is still uncertain, but it is suggested that during convalescence there is frequent

reinvasion of the blood stream by bacteria from the tissues and that if this occurs to a sufficient extent relapse will result. A possible explanation of the action of chloramphenicol in potentiating relapse is that it increases the survival rate of bacteria in the tissues by preventing their growth. Bacteria not actively growing are resistant to the action of chloramphenicol and it is possible that they are also resistant to the normal defence mechanisms of the host.

A complication observed in about one quarter of the patients during convalescence was the recurrence of low-grade symptomless pyrexia of variable duration. This "post-treatment pyrexia" may be an intermediate stage between uneventful convalescence and full-blown relapse, caused by the same factors as produce relapse.

There was no uniformity in the immunisation history of patients, and only a few had received vaccine within the previous 3 years. Immunised persons, however, had a much less severe illness than other patients. This difference was most marked in older men immunised before the Second World War and was not found in those immunised during or just after the Second World War. The potency of the vaccines used may be the cause of this difference in long-term effect,

and further research with this in mind might produce a vaccine capable of conferring life-long protection. The effect of combined oral and parenteral vaccine should also be further explored. Previous immunisation also diminished the incidence of isolation of bacteria both during the acute illness and during convalescence. This probably results from increased destruction of bacteria within the host.

There were 18 symptomless excreters and 4 cases of symptomless bacteraemia. The probable explanation of symptomless infection is that only a few bacteria penetrate the local barrier in the regional lymphatic tissues. This theory is supported by the low or absent serological response observed in such cases in Aberdeen.

Different types of antibody response were distinguished by serological assays performed for diagnosis, on discharge, and until 6 months after discharge from hospital. Some patients had no demonstrable serum antibodies. These patients were less severely ill although all were proved to have typhoid fever. Some other patients had their highest level of serum agglutination after discharge, and most of these had been given more than one course of antibiotic therapy. This may have suppressed antibody production until the antibiotic was withdrawn. These findings, however, must be accepted with caution, since

serological assays were not performed at regular intervals.

The pathogenesis of the carrier state is not yet understood, but it is proposited that there are two types of carrier. In one there is a focus of inflammation at the time of the acute illness which acts as a medium for persistent bacteria. In the second type there is no obvious lesion. Blood or bile may be frequently reinfected by invasion of bacteria from one diffusely infected organ, or from several localised but undetected foci. In chronic carriers without overt pathology bacteria may exist intracellularly in an inactive form which neither damages nor is injured by the host cell. Clinical evidence points to the liver as a possible site of chronic infection. Large numbers of bacteria may thus reach faeces from bile without causing systemic reaction. Much research is required to substantiate these hypotheses.

A clinical trial of ampicillin was conducted in early convalescent excreters to assess its possible value in preventing the chronic carrier state. There was a barely significant result in favour of ampicillin, but further trials timed differently and in other dosages are needed before the value of ampicillin in this context is established.

Persistent excreters were given ampicillin for 3 months, which may have influenced the low chronic carrier rate. Four of 6 possible chronic carriers have abnormal gall-bladder function. None of these patients has so far responded to prolonged ampicillin therapy or to cephaloridine.

The problems of typhoid fever are no longer to prevent its spread in crowded communities and to reduce its mortality rate. Attention must now be directed to a wider field of epidemiology and to a better understanding of the aetiology of the carrier state.

1. (A) COMPARISON OF NUMBER OF INOCULATED AND UNINOCULATED PATIENTS IN BACTERIOLOGICALLY AND IN CLINICALLY CONFIRMED GROUPS

	DIAGNOSTIC		TOTALS
	BACTERIOLOGICAL	CLINICAL	
INOCULATED	61 (76)	28 (13)	89
UNINOCULATED	342 (327)	38 (53)	380
ALL CONFIRMED CASES:	403	66	469

$\chi^2 = 25.72$ D.F. = 1 $P < 0.0005$ - HIGHLY SIGNIFICANT

(B) COMPARISON OF NUMBER OF INOCULATED AND UNINOCULATED PATIENTS IN CLINICALLY CONFIRMED AND IN UNCONFIRMED GROUPS

	DIAGNOSTIC GROUP		TOTALS
	CLINICALLY CONFIRMED	UNCONFIRMED	
INOCULATED	28 (37)	30 (21)	58
UNINOCULATED	38 (29)	8 (17)	46
TOTALS:	66	38	104

$\chi^2 = 11.60$ D.F. = 1 $P < 0.001$ - HIGHLY SIGNIFICANT.

2.A INCUBATION PERIODS - 378 "FOOD-EATERS"

DAYS	ALL PATIENTS	CHILDREN	ADULTS	RELAPSES	NON-RELAPSES	"T.A.B."	"NON-"T.A.B."	EXCRETERS	NON-EXCRETERS
2	2	0	2	0	2	1	1	0	2
3	3	0	3	0	3	0	3	2	1
4	7	2	5	2	5	2	5	2	5
5	17	4	13	4	13	1	16	7	10
6	25	2	23	5	20	5	20	10	15
7	23	3	20	7	16	7	16	9	14
8	27	6	21	8	19	3	24	10	17
9	33	4	29	8	25	1	32	15	18
10	31	6	25	7	24	7	24	12	19
11	16	3	13	3	13	4	12	4	12
12	21	3	18	6	15	1	20	9	12
13	19	2	17	4	15	4	15	6	13
14	27	8	19	4	23	4	23	11	16
15	14	6	8	6	8	4	10	5	9
16	17	4	13	6	11	0	17	8	9
17	10	1	9	3	7	1	9	5	5
18	18	9	9	4	14	1	17	8	10
19	7	2	5	1	6	1	6	3	4
20	8	2	6	1	7	1	7	0	8
21	5	2	3	0	5	0	5	0	5
22	11	1	10	1	10	3	8	5	6
23	4	1	3	3	1	0	4	2	2
24	5	0	5	1	4	0	5	3	2
25	4	2	2	0	4	0	4	1	3
26	5	0	5	1	4	1	4	2	3
27	5	0	5	0	5	1	4	1	4
28	5	1	4	0	5	2	3	2	3
29	0	0	0	0	0	0	0	0	0
30	3	1	2	1	2	2	1	1	2
31	1	1	0	0	1	0	1	0	1
34	2	1	1	0	2	0	2	0	2
35	1	0	1	0	1	0	1	1	0
38	1	0	1	0	1	0	1	0	1
39	1	1	0	0	1	0	1	1	0
TOTALS:	378	78	300	86	292	57	321	144	234
MEANS:	13.1	14.4	12.8	12.2	13.4	12.8	13.1	12.9	13.2

2.B.

INCUBATION PERIODS RELATED TO THE SEVERITY OF THE INITIAL INFECTION

(PROPORTIONS OF EACH INCUBATION PERIOD ARE SHOWN IN BRACKETS)

INCUBATION PERIOD (DAYS)	SEVERITY OF INITIAL INFECTION				TOTAL
	0 + 1		2 + 3		
2 - 7	15	(.2)	62	(.8)	77
8 - 14	31	(.2)	143	(.8)	174
15 - 21	10	(.1)	69	(.9)	79
OVER 21	18	(.4)	30	(.6)	48
TOTAL:	74	(.2)	304	(.8)	378

3.A - SEVERITY OF ILLNESS - AGE/SEX DISTRIBUTION

SEVERITY:	0	1	2	3	TOTALS
BOTH SEXES:					
0 - 14 YEARS	6	11	20	71	108
15 - 29 "	8	15	14	89	126
30 - 44 "	3	18	14	40	75
45 - 59 "	6	18	14	48	86
60 & OVER	5	12	12	45	74
ALL AGES:	28	74	74	293	469
% OF 469:	6.0	15.8	15.8	62.4	100.0
MALES:					
0 - 14 YEARS	5	6	6	36	53
15 - 29 "	4	6	3	24	37
30 - 44 "	2	9	9	17	37
45 - 59 "	4	8	6	8	26
60 & OVER	3	8	3	15	29
ALL AGES:	18	37	27	100	182
% OF 182:	9.9	20.3	14.8	55.0	100.0
FEMALES:					
0 - 14 YEARS	1	5	14	35	55
15 - 29 "	4	9	11	65	89
30 - 44 "	1	9	5	23	38
45 - 59 "	2	10	8	40	60
60 & OVER	2	4	9	30	45
ALL AGES:	10	37	47	193	287
% OF 287	3.5	12.9	16.4	67.2	100.0

TYPHOID FEVER

3.B THE "SEVERITY OF THE ILLNESS" IN ALL PATIENTS, DISTINGUISHING SEX

ABERDEEN, 1964

SEVERITY:	"0"	"1"	"2"	"3"	TOTALS
MALES (ALL AGES)	18 (11)	37 (29)	27 (29)	100 (113)	182
FEMALES (ALL AGES)	10 (17)	37 (45)	47 (45)	193 (180)	287
BOTH SEXES:	28	74	74	293	469

$\chi^2 = 11.94$ D.F. = 3 $P < 0.01$ SIGNIFICANT

THE SEX DISTRIBUTION OF THE "SEVERITY OF THE ILLNESS" IN ALL PATIENTS, DISTINGUISHING AGE GROUPS

AGE GROUP:	0 - 14		15 - 29		30 - 44		45 - 59		60 AND OVER	
SEVERITY:	0 + 1	2 + 3	0 + 1	2 + 3	0 + 1	2 + 3	0 + 1	2 + 3	0 + 1	2 + 3
MALES	11 (8)	42 (45)	10 (7)	27 (30)	11 (10)	26 (27)	12 (7)	14 (19)	11 (7)	18 (22)
FEMALES	6 (9)	49 (46	13 (16)	76 (73)	10 (11)	28 (27)	12 (17)	48 (43)	6 (10)	39 (35)
BOTH SEXES:	17	91	23	103	21	54	24	62	17	57

χ^2 TESTS: 0 - 14) 15 - 29) No significant difference. 30 - 44)

45 - 59 - $\chi^2 = 4.94$, D.F. = 1, $P < 0.05$ - possibly significant

60 & over - $\chi^2 = 4.72$, D.F. = 1, $P < 0.05$ - possibly significant.

3.c

THE SEVERITY OF THE ILLNESS IN UNINOCULATED ADULTS, DISTINGUISHING SEX

ABERDEEN OUTBREAK OF TYPHOID FEVER, 1964

SEX	15 - 29		30 - 44		45 - 59		60 & OVER		TOTALS	
	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3
MALES	4	23	0	8	4	7	0	12	8	50
FEMALES	10	70	10	26	11	44	5	37	36	177
BOTH SEXES:	14	93	10	34	15	51	5	49	44	227

NO SIGNIFICANT DIFFERENCES BETWEEN THE SEXES WERE DEMONSTRATED IN ANY AGE GROUP.

3.D

MEAN

COMPARISON OF THE/DURATION OF PYREXIA ON CHLORAMPHENICOL IN MODERATELY AND SEVERELY ILL PATIENTS

	MODERATE	SEVERE
NUMBERS	75	231
MEANS	4.2 DAYS	5.2 DAYS
S.E. DIFFERENCE	0.41	

t = 2.44 = P < 0.02 - SIGNIFICANT

3. E. - Severity of the Initial Infection in Patients who Relapsed compared with All Other Patients

SEE APPENDIX TO SECTION III

2.C

3.F. - Comparison of Convalescent Excreters and Other Patients on the basis of The Severity of the Initial Infection

SEE APPENDIX TO SECTION VII

3.A

4.A COMPLICATIONS

LINK No.	SEX	AGE	SEVERITY ON ADMISSION	INITIAL TREATMENT		DAYS OF ILLNESS BEFORE TREATMENT	DAYS OF PYREXIA ON TREATMENT	COMPLICATIONS	REMARKS
				ANTIBIOTIC	DAILY DOSE MG/KG				
271	M	10	3	CHLOR.	20	1	6	PNEUMONIA	
172	M	11	3	CHLOR.	39	5	7	MELAENA	
54	F	16	3	CHLOR.	33	10	5	PERIPHERAL NEURITIS	RELAPSED TWICE
255	F	17	3	CHLOR.	42	4	5	EFFUSION, LEFT SHOULDER	
137	F	19	3	CHLOR.	26	5	4	PERIPHERAL NEURITIS	
261	M	21	3	CHLOR.	29	9	5	PNEUMONIA	TAB. RELAPSED
189	F	22	3	CHLOR.	35	3	3	PERIPHERAL NEURITIS	
84	F	22	2	CHLOR.	41	12	3	EFFUSION SHOULDERS MYOSITIS.	RELAPSED
214	F	24	3	CHLOR.	36	7	5	PERIPHERAL NEURITIS	
209	F	25	3	CHLOR.	30	10	6	CHOLECYSTITIS	RELAPSED; NO POSITIVE ISOLATION
317	F	35	3	CHLOR.	35	7	6	PERIPHERAL NEURITIS	
37	F	38	3	CHLOR.	32	6	0	PERIPHERAL NEURITIS	
306	F	31	3	CHLOR.	37	12	4	DEEP VENOUS THROMBOSIS CHOLECYSTITIS PERIPHERAL NEURITIS	TAB. RELAPSED.
455	M	43	3	CHLOR.	34	7	8	DEEP VENOUS THROMBOSIS PULMONARY EMBOLUS	TAB. RELAPSED.
531	F	46	3	CHLOR.	28	31	5	DEEP VENOUS THROMBOSIS PULMONARY EMBOLUS.	ADMITTED WITH PULMONARY EMBOLUS.
304	F	48	3	CHLOR.	26	3	12	PULMONARY EMBOLUS	
231	F	48	3	CHLOR.	24	14	10	PNEUMONIA	
82	F	49	3	CHLOR.	32	14	5	PHLEBITIS	
297	F	49	2	CHLOR.	40	3	6	MYOCARDITIS	
24	F	49	2	CHLOR.	25	7	7	DEEP VENOUS THROMBOSIS	
95	F	55	3	MIXED		7	17	CORONARY THROMBOSIS	RELAPSED
387	M	55	3	CRYSTAPEN		10	4	PNEUMONIA	
415	F	58	3	CHLOR.	28	5	6	DEEP VENOUS THROMBOSIS	RELAPSED
129	M	59	2	CHLOR.	16	7	4	DEEP VENOUS THROMBOSIS PULMONARY EMBOLUS.	
134	F	60	3	CHLOR.	26	12	5	DEEP VENOUS THROMBOSIS PULMONARY EMBOLUS MYOCARDITIS.	
229	F	60	3	CHLOR.	33	15	8	PULMONARY EMBOLUS	RELAPSED; DIED.
207	F	60	3	CHLOR.	33	1	8	MYOCARDITIS	
264	F	60	3	CHLOR.	-	-	-	CORONARY THROMBOSIS	DIED
177	M	61	3	CHLOR.	27	0	9	DEEP VENOUS THROMBOSIS	
41	F	61	3	CHLOR.	63	0	6	EFFUSION OF LEFT KNEE	
48	F	62	2	CHLOR.	27	9	5	CHOLECYSTITIS	RELAPSED;CARRIER
238	M	62	3	CHLOR.	28	6	4	PULMONARY EMBOLUS	
125	F	63	3	CHLOR.	35	8	4	PERIPHERAL NEURITIS	RELAPSED
44	F	64	1	CHLOR.	39	23	1	CHOLECYSTITIS	
535	M	65	2	CHLOR.	27	0	15	SPINAL OSTEOMYELITIS CHOLECYSTITIS	TAB. RELAPSED
403	F	67	2	CHLOR.	32	10	4	DEEP VENOUS THROMBOSIS	RELAPSED
538	F	69	3	CHLOR.	34	8	2	CEREBRAL THROMBOSIS	RELAPSED
111	F	69	2	CHLOR.	39	13	4	PHLEBITIS	
428	F	69	3	CHLOR.	26	5	14	CHOLECYSTITIS	RELAPSED
524	M	70	1	CHLOR.	29	11	2	PHLEBITIS	
93	M	71	1	CHLOR.	29	7	2	PNEUMONIA	
360	F	72	3	CHLOR.	35	8	9	PNEUMONIA	RELAPSED
9	F	74	3	CHLOR.	39	9	14	TYPHOID ULCER R.LEG	RELAPSED
140	M	76	2	CHLOR.	19	20	7	PULMONARY EMBOLUS	
420	M	76	1	CHLOR	21	0	3	PNEUMONIA	DIED
477	F	77	1	CHLOR.	41	17	2	DEEP VENOUS THROMBOSIS	
58	F	79	3	CHLOR.	55	9	3	TENDER TOES.M.P.JOINTS	
340	F	82	2	CHLOR.	24	1	21	PULMONARY EMBOLUS	

4.(B) AGE DISTRIBUTION OF 48 PATIENTS WITH COMPLICATIONS

	0 - 14	15 - 29	30 - 44	45 - 59	60 & OVER	ALL AGES
COMPLICATIONS	2 (11)	8 (13)	4 (8)	10 (9)	24 (7)	48
OTHERS	106 (97)	118 (113)	71 (67)	76 (77)	50 (67)	421
TOTALS:	108	126	75	86	74	469

χ^2 = 53.34 WITH YATES CORRECTION D.F. = 4 P < 0.00050 - HIGHLY SIGNIFICANT.

4.(C) COMPARISON OF MEAN DURATION OF PYREXIA ON CHLORAMPHENICOL IN CASES WITH COMPLICATIONS AND OTHER CASES

	"SEVERE" COMPLICATIONS	OTHER "SEVERE" CASES
NOS.	30	201
MEANS	6.3 DAYS	5.0 DAYS

S.E. DIFFERENCE 0.53

t = 2.45

P < 0.02 - SIGNIFICANT

	"MODERATE" COMPLICATIONS	OTHER "MODERATE" CASES
NOS.	10	65
MEANS	7.6 DAYS	3.6 DAYS

S.E. DIFFERENCE 1.45

t = 2.76

P < 0.01 - SIGNIFICANT

1. Treatment in the Initial Illness

(A) Comparison of the mean duration of pyrexia in children on Chloramphenicol and on Ampicillin.

	Chloramphenicol	Ampicillin
Numbers	58	25
Means	4.4 days	8.3 days

S.E. difference 0.98

$t = 3.98$

$P < 0.01$ = highly significant

(B) The relapse rate in children on Chloramphenicol and on Ampicillin.

Drug	Numbers	Number who relapsed	Relapse Rate
Chloramphenicol	58	11	19.0%
Ampicillin	25	0	0

(C) Comparison of the mean duration of pyrexia in children on the two mixed treatments

	Chloramphenicol followed by Ampicillin	Ampicillin followed by Chloramphenicol
Numbers	12	10
Means	3.7 days	12.6 days

S.E. difference 1.52

$t = 5.86$

$P < 0.01$ = highly significant

2.A - DETAILS OF 86 PATIENTS WHO RELAPSED - ABERDEEN TYPHOID OUTBREAK, 1964

LINK No.	SEX	AGE	SEVERITY OF INITIAL ILLNESS	INITIAL TREATMENT		DAYS OF ILLNESS BEFORE TREATMENT	DAYS OF PYREXIA ON TREATMENT	DAYS FROM END OF TREATMENT TO RELAPSE	DAYS FROM END OF PYREXIA TO RELAPSE	DAYS OF ILLNESS ON RELAPSE	LEVEL OF SERUM AGGLUTINATION										REMARKS
											BEFORE TREATMENT		ON RELAPSE		ON DISCHARGE		AT THREE MONTHS		AT SIX MONTHS		
				ANTIBIOTIC	DAILY DOSAGE MG/KG.						'H'	'O'	'H'	'O'	'H'	'O'	'H'	'O'	'H'	'O'	
31	M	3	3	CHLOR.	36	8	5	9	16	27	1:25	-	-	-	1:25	NIL	NIL	1:100	-	-	
522	F	5	3	CHLOR.	32	6	4	21	32	41	1:200	-	-	-	1:100	NIL	1:100	NIL	1:50	1:200	EXCRETER
321	F	6	3	MIXED		7	21	10	13	46	1:25	-	-	-	NIL	NIL	NIL	NIL	NIL	NIL	
283	M	6	3	CHLOR.	43	4	6	12	20	30	1:50	-	NIL	NIL	NIL	NIL	NIL	NIL	NIL	NIL	
512	M	7	3	MIXED		9	5	11	20	37	1:100	NIL	-	-	1:400	NIL	1:50	NIL	-	-	
69	M	8	2	MIXED		11	2	11	24	44	1:25	-	1:25	NIL	1:400	1:50	1:50	NIL	1:25	NIL	EXCRETER
151	F	8	2	CHLOR.	36	1	2	10	20	23	NIL	-	NIL	NIL	1:400	NIL	NIL	NIL	NIL	NIL	EXCRETER
502	M	8	3	CHLOR.	34	1	7	11	18	35	NIL	-	NIL	NIL	NIL	NIL	-	-	-	-	
241	F	9	3	MIXED		5	10	13	38	51	1:100	-	1:50	NIL	1:100	NIL	1:25	NIL	1:25	NIL	
493	M	10	3	CHLOR.	19	6	7	11	19	32	1:25	-	-	-	1:25	NIL	NIL	NIL	NIL	NIL	EXCRETER
63	F	11	1	CHLOR.	22	9	2	9	21	32	1:50	-	-	-	1:100	NIL	NIL	NIL	NIL	NIL	
274	F	12	3	CHLOR.	29	4	2	9	20	26	1:50	-	-	-	1:100	NIL	1:50	NIL	1:25	1:100	EXCRETER
7	F	13	3	CHLOR.	36	2	5	20	29	37	1:100	-	1:100	NIL	NIL	NIL	1:50	NIL	NIL	NIL	
203	F	13	3	CHLOR.	41	6	4	13	23	33	1:400+	-	1:200	NIL	1:400	1:25	1:25	NIL	NIL	1:25	EXCRETER
222	M	13	3	CHLOR.	26	2	5	21	30	37	1:50	-	-	-	NIL	NIL	NIL	NIL	1:50	NIL	
45	F	15	3	CHLOR.	35	7	3	15	26	36	NIL	-	1:25	-	1:100	NIL	1:25	NIL	NIL	1:25	
81	F	15	3	CHLOR.	38	2	5	9	18	25	1:25	-	1:50	NIL	NIL	NIL	NIL	NIL	NIL	NIL	EXCRETER
133	F	15	3	CHLOR.	34	7	12	9	12	31	1:400+	-	1:50	NIL	NIL	NIL	NIL	NIL	NIL	NIL	
225	F	16	3	CHLOR.	29	6	4	13	25	34	1:25	-	-	-	1:25	1:25	1:50	NIL	1:25	1:400	
54	F	16	3	CHLOR.	33	10	5	12	21	31	1:100	-	-	-	1:50	1:50	1:25	NIL	NIL	1:100	
96	F	18	3	CHLOR.	44	7	4	11	21	33	1:1600+	-	1:100	NIL	1:50	NIL	NIL	NIL	NIL	NIL	
414	M	20	3	CHLOR.	24	9	4	14	24	37	1:100	-	-	-	NIL	NIL	1:25	NIL	-	-	
343	M	20	3	CHLOR.	26	4	4	13	23	31	1:50	NIL	1:25	NIL	NIL	NIL	NIL	NIL	NIL	1:50	
261	M	21	3	CHLOR.	29	9	5	23	23	46	1:25	NIL	1:25	NIL	1:25	1:50	-	-	NIL	1:100	INOCULATED
204	F	22	3	CHLOR.	31	10	7	11	18	35	1:25	-	1:25	NIL	1:25	NIL	NIL	NIL	NIL	NIL	EXCRETER
84	F	22	2	CHLOR.	34	12	3	13	22	41	NIL	-	NIL	NIL	NIL	NIL	NIL	NIL	NIL	1:25	
209	F	25	3	CHLOR.	30	10	6	38	46	60	1:25	-	NIL	1:50	NIL	NIL	NIL	1:25	-	-	
236	M	25	3	CHLOR.	39	8	5	14	23	36	1:1600+	-	-	-	1:100	NIL	1:25	NIL	-	-	
215	F	26	3	CHLOR.	38	3	4	11	21	28	1:200	-	1:50	NIL	1:25	NIL	1:50	NIL	NIL	NIL	
422	M	26	3	CHLOR.	25	4	4	18	29	54	1:100	NIL	1:800	NIL	1:1600	NIL	1:25	NIL	1:25	NIL	EXCRETER
190	F	26	3	CHLOR.	32	5	9	9	14	63	NIL	-	-	-	1:800	NIL	1:200	NIL	1:100	1:100	EXCRETER
471	F	26	3	CHLOR.	31	1	5	10	19	25	NIL	-	NIL	NIL	NIL	1:50	NIL	NIL	NIL	1:200	
275	M	27	3	CHLOR.	24	3	4	19	29	36	1:50	-	1:50	NIL	1:25	1:25	1:25	1:50	NIL	1:200	INOCULATED
295	F	28	3	CHLOR.	42	6	4	12	20	30	NIL	-	NIL	-	NIL	NIL	NIL	NIL	NIL	1:50	
407	F	28	3	CHLOR.	25	14	3	8	19	36	1:25	NIL	-	-	1:200	1:50	1:50	NIL	NIL	1:25	
489	F	29	2	CHLOR.	35	10	3	12	23	35	1:25	-	NIL	-	1:25	NIL	NIL	NIL	NIL	NIL	
530	M	29	2	CHLOR.	27	7	2	12	24	34	1:50	-	-	-	1:1600	NIL	1:1600	NIL	1:3200	1:200	EXCRETER; INOCULATED.
309	M	29	2	CHLOR.	18	7	3	14	25	35	1:50	-	NIL	NIL	NIL	NIL	NIL	NIL	NIL	NIL	
312	M	29	3	CHLOR.	25	2	6	16	24	32	NIL	-	-	-	1:100	NIL	1:25	NIL	NIL	NIL	
273	M	29	1	CHLOR.	21	5	1	13	26	32	1:50	-	-	-	1:100	NIL	1:100	NIL	1:100	NIL	INOCULATED
176	F	30	3	CHLOR.	26	13	4	19	29	46	1:100	NIL	1:25	NIL	1:25	NIL	1:25	NIL	NIL	-	EXCRETER
82	F	30	3	CHLOR.	30	4	7	13	20	32	1:50	-	1:50	NIL	1:50	1:320	1:20	1:80	NIL	1:50	EXCRETER
306																					

DETAILS OF 86 PATIENTS WHO RELAPSED - ABERDEEN TYPHOID OUTBREAK, 1964. (CONTD.)

LINK NO.	SEX	AGE	SEVERITY OF INITIAL ILLNESS	INITIAL TREATMENT		DAYS OF ILLNESS BEFORE TREATMENT	DAYS OF PYREXIA ON TREATMENT	DAYS FROM END OF TREATMENT TO RELAPSE	DAYS FROM END OF PYREXIA TO RELAPSE	DAYS OF ILLNESS ON RELAPSE	LEVEL OF SERUM AGGLUTINATION								REMARKS
											BEFORE TREATMENT		ON RELAPSE		ON DISCHARGE		AT THREE MONTHS		AT SIX MONTHS		
				ANTIBIOTIC	DAILY DOSAGE MG/KG						'H'	'O'	'H'	'O'	'H'	'O'	'H'	'O'	'H'	'O'	
306	F	31	3	CHLOR.	37	12	4	5	11	27	1:100	-	-	-	1:25	NIL	1:25	1:100	NIL	1:200	INOCULATED
442	M	31	3	CHLOR.	31	9	11	18	21	41	1:200	-	1:25	NIL	NIL	NIL	NIL	NIL	NIL	NIL	
22	M	32	3	CHLOR.	19	10	8	8	14	33	NIL	-	-	-	1:6400	NIL	1:800	NIL	1:100	NIL	EXCRETER
486	F	32	3	CHLOR.	33	8	5	12	21	34	1:200	-	-	-	1:200	NIL	1:50	NIL	NIL	NIL	EXCRETER
72	F	34	2	CHLOR.	23	9	3	8	19	32	1:100	-	-	-	NIL	NIL	1:1600	NIL	-	-	CARRIER
357	M	34	3	CHLOR.	21	10	3	12	23	35	1:25	-	1:25	NIL	1:25	NIL	NIL	NIL	NIL	NIL	INOCULATED
367	M	36	3	CHLOR.	19	8	6	14	22	36	1:50	NIL	-	-	1:25	NIL	NIL	1:50	NIL	1:100	
75	M	37	3	CHLOR.	28	5	3	14	25	33	1:1000	NIL	1:800	NIL	1:400	NIL	1:100	NIL	NIL	1:50	INOCULATED
184	F	37	3	CHLOR.	40	0	5	13	22	32	1:200	-	1:25	NIL	1:100	NIL	NIL	NIL	NIL	1:100	EXCRETER
508	F	37	3	CHLOR.	24	2	4	12	21	28	1:50	-	-	-	1:50	NIL	NIL	NIL	NIL	1:50	
509	F	38	3	CHLOR.	25	2	3	8	19	23	NIL	-	NIL	NIL	1:25	1:100	-	-	-	-	EXCRETER
474	F	39	2	CHLOR.	31	6	3	12	23	33	1:1600	NIL	1:200	NIL	1:200	1:100	NIL	NIL	NIL	1:50	
160	M	39	1	CHLOR.	24	9	0	14	28	37	1:50	NIL	1:50	NIL	1:50	NIL	1:100	NIL	1:100	NIL	INOCULATED
6	F	43	3	CHLOR.	33	5	10	19	27	44	1:1600	NIL	-	-	1:50	NIL	1:100	NIL	1:25	NIL	
455	M	43	3	CHLOR.	34	7	8	(95)	(103)	(120)	1:800	NIL	1:400	NIL	1:400	-	1:800	1:50	1:400	1:50	INOCULATED
13	F	44	3	CHLOR.	36	4	0	15	23	31	1:200	-	1:200	NIL	1:25	NIL	NIL	NIL	NIL	NIL	EXCRETER
242	F	44	3	CHLOR.	31	8	3	10	21	32	1:25	-	-	-	NIL	NIL	NIL	NIL	1:25	NIL	
35	F	45	3	CHLOR.	34	6	9	19	26	41	1:200	-	1:25	—	1:200	NIL	NIL	NIL	NIL	1:100	
456	F	50	2	CHLOR.	20	8	3	9	21	33	1:800	-	-	-	1:100	NIL	1:25	NIL	NIL	1:50	EXCRETER
122	F	54	3	CHLOR.	26	0	6	12	20	31	1:25	-	-	-	1:200	NIL	1:50	NIL	NIL	NIL	EXCRETER
270	F	55	3	CHLOR.	24	6	11	16	19	36	NIL	NIL	-	-	1:1600	NIL	1:400	NIL	1:100	NIL	
95	F	55	3	MIXED		7	17	10	17	36	1:200	-	-	-	1:25	NIL	-	1:25	NIL	NIL	
8	F	56	3	CHLOR.	34	7	3	16	27	38	1:100	-	1:50	NIL	1:3200	NIL	1:200	NIL	1:50	NIL	EXCRETER
17	M	56	3	CHLOR.	24	8	3	21	32	43	1:100	-	1:25	NIL	1:800	NIL	1:400	1:50	1:50	NIL	EXCRETER; INOCULATED
415	F	58	3	CHLOR.	28	5	6	35	44	55	1:1000	1:25	1:12800	NIL	1:800	1:800	1:400	NIL	1:200	1:200	EXCRETER
106	F	59	2	CHLOR.	27	6	3	8	17	26	NIL	-	NIL	NIL	1:400	NIL	1:50	NIL	1:25	1:25	
345	M	60	2	CHLOR.	24	14	6	8	16	36	1:25	-	1:25	NIL	1:200	NIL	-	-	-	-	EXCRETER
229	F	60	3	CHLOR.	33	15	8	6	14	35	1:50	-	1:25	-	DIED.						
48	F	62	2	CHLOR.	26	9	5	8	17	31	1:100	-	-	-	1:400	NIL	1:50	NIL	1:200	NIL	CARRIER
351	M	62	2	CHLOR.	24	12	4	11	21	37	1:500	-	-	-	1:400	NIL	1:50	NIL	NIL	NIL	
239	F	62	2	CHLOR.	28	9	3	21	33	45	1:400	-	1:25	NIL	NIL	NIL	NIL	NIL	NIL	1:25	
472	M	63	2	CHLOR.	26	14	3	12	23	40	1:50	-	-	-	1:25	NIL	NIL	NIL	-	-	
125	F	63	3	CHLOR.	34	8	4	12	22	35	1:50	-	-	-	NIL	NIL	NIL	NIL	NIL	NIL	
535	M	65	2	CHLOR.	27	0	15	4	0	?	1:1600	NIL	1:600	NIL	1:1600	NIL	1:1600	NIL	1:2800	1:200	INOCULATED
291	F	67	3	CHLOR.	19	7	8	7	15	30	NIL	-	NIL	-	1:200	NIL	1:800	NIL	1:400	NIL	CARRIER
403	F	67	2	CHLOR.	31	10	4	18	29	74	1:100	-	1:12800	1:100	1:800+	NIL	1:400	NIL	1:100	1:100	EXCRETER
55	M	69	3	CHLOR.	26	6	11	8	11	40	1:400	-	-	-	1:200	NIL	1:100	NIL	-	-	INOCULATED
111	F	69	2	CHLOR.	39	13	4	22	32	43	1:200	-	1:25	NIL	1:25	1:25	NIL	NIL	-	-	
538	F	69	3	CHLOR.	34	8	2	8	16	26	1:1600	NIL	1:1600	NIL	1:800	NIL	1:1600	NIL	-	-	EXCRETER
428	F	69	3	CHLOR.	26	5	14	10	10	29	1:50	NIL	-	-	1:200	NIL	1:50	NIL	NIL	NIL	EXCRETER
537	M	72	2	MIXED		10	14	11	11	35	1:200	-	-	-	1:25	NIL	NIL	NIL	NIL	NIL	
360	F	72	3	CHLOR.	35	8	9	14	19	36	NIL	NIL	1:1600	1:25	1:200	1:50	1:50	NIL	-	-	
9	F	74	3	CHLOR.	39	9	14	4	6	30	1:25	-	NIL	NIL	NIL	NIL	NIL	NIL	NIL	NIL	
523	F	76	3	CHLOR.	39	0	5	14	23	44	1:400+	-	-	-	1:1600	NIL	1:1600	NIL	1:50	NIL	EXCRETER

2. B-The Age Distribution of Patients who Relapsed - Aberdeen, 1964

Age:	0 - 14	15 - 29	30 - 44	45 - 59	60 & over	Totals
Relapses	15 (20)	25 (23)	19 (14)	9 (16)	18 (13)	86
Others	93 (88)	101 (103)	56 (61)	77 (70)	56 (61)	383
Totals:	108	126	75	86	74	469

$\chi^2 = 8.26$. D.F. = 4 Not significant.

2. C-The Severity of the Initial Infection in Patients who Relapsed Compared with that of Other Patients

	Mild	Moderate	Severe	Totals
Relapses	3 (20)	19 (17)	64 (49)	86
Others	106 (89)	72 (74)	205 (220)	383
Totals:	109	91	269	469

$\chi^2 = 22.08$. D.F. = 1 $P < 0.00050$
Highly significant.

2. - PATIENTS WHO RELAPSED

(D) DURATION OF PYREXIA OF ALL PATIENTS ON CHLORAMPHENICOL DISTINGUISHING PATIENTS WHO RELAPSED

	RELAPSE	OTHER
NUMBER	80	310
MEAN (DAYS)	5.2	4.1
S.E. DIFFERENCE	0.40	
	t = 2.75	
	$P <$ 0.01 = HIGHLY SIGNIFICANT	

(E) DURATION OF PYREXIA ON CHLORAMPHENICOL OF PATIENTS WHO HAD A SEVERE INITIAL INFECTION, DISTINGUISHING PATIENTS WHO RELAPSED.

	RELAPSE	OTHER
NUMBER	60	171
MEAN (DAYS)	5.8	5.0
S.E. DIFFERENCE	0.40	
	t = 2.00	
	$P <$ 0.05 = SIGNIFICANT	

(F) DURATION OF PYREXIA ON CHLORAMPHENICOL OF PATIENTS WHO HAD A MODERATE INITIAL INFECTION, DISTINGUISHING PATIENTS WHO RELAPSED

	RELAPSE	OTHER
NUMBER	17	58
MEAN (DAYS)	4.1	4.2

NO DIFFERENCE

2. PATIENTS WHO RELAPSED

(G) COMPARISON OF THE MEAN DAYS OF ILLNESS BEFORE CHLORAMPHENICOL BETWEEN SEVERELY ILL CHILDREN WHO RELAPSED AND THOSE WITH A NORMAL CONVALESCENCE

	CHILDREN WHO RELAPSED	CHILDREN WITH A NORMAL CONVALESCENCE
NUMBERS	9	10
MEAN	4.3 DAYS	8.9 DAYS
S.E. DIFFERENCE	1.94	

$t = 2.37$

$P < 0.05$ -- POSSIBLY SIGNIFICANT

3. - Comparison of Patients who had Post-Treatment Pyrexia (P.T.P.) with other Typhoid Patients

A. Age Distribution

	0 - 14	15 - 29	30 - 44	45 - 59	60+	All ages
P.T.P.	47 (29)	26 (33)	12 (20)	20 (23)	20 (20)	125
Others	61 (79)	100 (93	63 (55	66 (63)	54 (54)	344
Totals:	108	126	75	86	74	469

$\chi^2 = 20.37$ D.F. = 4 $P < 0.00050$ - Highly significant

B. Incidence of Relapse

	Relapse	Non-Relapse	Totals
P.T.P.	12 (23)	113 (102)	125
Others	74 (63)	270 (281)	344
Totals	86	383	469

$\chi^2 = 7.91$ D.F. = 1 $P < 0.0050$ - significant

C. Number of Convalescent Excreters

	Excreters	Others	Totals
P.T.P.	53 (42)	72 (83)	125
Others	106 (117)	238 (227)	344
Totals	159	310	469

$\chi^2 = 4.99$ D.F. = 1 $P < 0.05$ - possibly significant

3. - Comparison of Patients who had Post-Treatment Pyrexia (P.T.P.) with other Typhoid Patients

D. The distribution of the severity of the initial infection

	Mild	Moderate	Severe	Totals
P.T.P.	19 (29)	18 (24)	88 (72)	125
Others	90 (80)	73 (67)	181 (197)	344
Totals	109	91	269	469

$\chi^2 = 10.51$ D.F. = 2 $P < 0.001$ = significant.

E. Number treated initially with chloramphenicol

	On initial chloramphenicol	Other antibiotic	Total treated
P.T.P.	97 (107)	28 (18)	125
Others	293 (283)	36 (46)	329
Totals	390	64	454

$\chi^2 = 8.90$ D.F. = 1 $P < 0.0050$ = significant.

F. Number of inoculated adults

	Inoculated	Uninoculated	Totals
Adults with P.T.P.	9 (19)	69 (59)	78
Other adults	81 (71)	202 (212)	283
All adults	90	271	361

$\chi^2 = 8.64$ D.F. = 1 $P < 0.0050$ = significant.

4. COMPARISON OF CHILDREN WITH POST-TREATMENT PYREXIA (P.T.P.) WITH OTHER CHILDREN

A. INCIDENCE OF RELAPSE

	RELAPSE	NON-RELAPSE	TOTALS
P.T.P.	1 (7)	46 (40)	47
OTHER CHILDREN	14 (8)	47 (53)	61
TOTALS	15	93	108

$\chi^2 = 7.96$ D.F. = 1 $P < 0.0050$ - SIGNIFICANT

B. NUMBER OF CONVALESCENT EXCRETERS

	EXCRETERS	OTHERS	TOTALS
P.T.P.	31 (22)	16 (25)	47
OTHER CHILDREN	19 (28)	42 (33)	61
TOTALS	50	58	108

$\chi^2 = 11.58$ D.F. = 1 $P < 0.001$ - HIGHLY SIGNIFICANT

C. THE DISTRIBUTION OF THE SEVERITY OF THE INITIAL INFECTION IN CHILDREN

	0 & 1	2 & 3	TOTALS
P.T.P.	3 (7)	44 (40)	47
OTHER CHILDREN	14 (10)	47 (51)	61
TOTALS	17	91	108

$\chi^2 = 4.32$ D.F. = 1 $P < 0.05$ - POSSIBLY SIGNIFICANT

1 - COMPARISON OF SEX DISTRIBUTION IN INOCULATED AND UNINOCULATED PATIENTS

(PROPORTIONS ARE SHOWN IN BRACKETS)

	MALES	FEMALES	ALL PATIENTS
INOCULATED	72 (.8)	15 (.2)	87
UNINOCULATED	108 (.3)	270 (.7)	378
TOTALS:	180	285	465

2 - COMPARISON OF AGE DISTRIBUTION IN INOCULATED AND UNINOCULATED ADULTS

	15 - 29	30 - 44	45 - 59	60 & OVER	ALL AGES
INOCULATED	16 (30)	31 (18)	20 (21)	19 (17)	86
UNINOCULATED	107 (93)	44 (57)	66 (65)	54 (56)	271
TOTALS:	123	75	86	73	357

$\chi^2 = 19.64$. D.F. = 3. $P < 0.00050$ - HIGHLY SIGNIFICANT.

3- COMPARISON OF DISTRIBUTION OF CONVALESCENT EXCRETERS IN INOCULATED AND UNINOCULATED ADULTS

	EXCRETERS	OTHERS	TOTAL
INOCULATED	14 (26)	72 (60)	86
UNINOCULATED	95 (83)	176 (188)	271
ALL ADULTS:	109	248	357

$\chi^2 = 9.98$. D.F. = 1. $P < 0.0050$ - SIGNIFICANT.

4.A - COMPARISON OF INOCULATED AND UNINOCULATED ADULTS ON THE BASIS OF THE "SEVERITY" OF THE ILLNESS

SEVERITY:	0 + 1	2 + 3	TOTAL
INOCULATED	40 (20)	46 (66)	86
UNINOCULATED	44 (64)	227 (207)	271
ALL ADULTS:	84	273	357

$\chi^2 = 31.59$. D.F. = 1. $P < 0.00050$ - HIGHLY SIGNIFICANT.

4.B

COMPARISON OF INOCULATED AND UNINOCULATED ADULTS ON THE BASIS OF THE "SEVERITY" OF THE ILLNESS, DISTINGUISHING AGE GROUPS

AGE:	15 - 29		30 - 44		45 - 59		60+		ALL AGES	
SEVERITY:	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3
INOCULATED	8	8	11	20	9	11	12	7	40	46
UNINOCULATED	14	93	10	34	15	51	5	49	44	227
ALL ADULTS:	22	101	21	54	24	62	17	56	84	273

PERCENTAGE OF "MILD" CASES IN EACH AGE GROUP

AGE:	15 - 29		30 - 44		45 - 59		60 & OVER	
	NO.	% MILD	NO.	% MILD	NO.	% MILD	NO.	% MILD
INOCULATED	16	50	31	35	20	45	19	63
UNINOCULATED	107	13	44	25	66	23	54	9

RESULTS:

15 - 29 YEARS	% "MILD"	S.E. DIFFERENCE
INOCULATED	50	12.9
UNINOCULATED	13	

DIFF/S.E. DIFF. = 2.87 - SIGNIFICANT. $P < 0.005$

60 YRS. & OVER	% "MILD"	S.E. DIFFERENCE
INOCULATED	63	11.7
UNINOCULATED	9	

DIFF/S.E. DIFF. = 4.62 - HIGHLY SIGNIFICANT. $P < 0.001$.

30 - 44 YEARS) NO SIGNIFICANT DIFFERENCE
45 - 59 YEARS) IN PROPORTIONS

4. C

COMPARISON OF ADULTS INOCULATED WITH PHENOLISED T.A.B. VACCINE WITH UNINOCULATED ADULTS ON THE BASIS OF THE "SEVERITY" OF THE ILLNESS, DISTINGUISHING AGE AND TIME GROUPS

YEARS:	1950-63		1940-49				1910-39		1910-63	
AGE:	15-29		30-44		45-59		60 +		ALL AGES	
SEVERITY:	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3
INOCULATED	8	6	7	9	8	9	11	7	34	31
UNINOCULATED	14	93	10	34	15	51	5	49	44	227
ALL ADULTS:	22	99	17	43	23	60	16	56	78	258

PERCENTAGE OF "MILD" CASES IN EACH AGE GROUP

YEARS:	1950 - 63		1940 - 49				1910 -1939	
AGE:	15 - 29		30 -44		45 - 59		60 +	
	No.	% MILD	No.	% MILD	No.	% MILD	No.	% MILD
INOCULATED	14	57	16	44	17	47	18	61
UNINOCULATED	107	13	44	23	66	23	54	9

RESULTS:

	15 - 29 YEARS	% MILD	S.E. DIFFERENCE
1950-63	INOCULATED	57	13.7
	UNINOCULATED	13	

DIFF./S.E. DIFF. = 3.21 = SIGNIFICANT - P < 0.005

	60 YEARS & OVER	% MILD	S.E. DIFFERENCE
1910-39	INOCULATED	61	12.1
	UNINOCULATED	9	

DIFF./S.E. DIFF. = 4.30 = HIGHLY SIGNIFICANT. P < 0.001

1940-49 30 - 44 YEARS) NO SIGNIFICANT DIFFERENCE
45 - 59 YEARS) IN PROPORTIONS

4 (D)

COMPARISON OF PATIENTS INOCULATED WITH ALCOHOLISED T.A.B. VACCINE WITH UNINOCULATED PATIENTS IN THE SAME AGE GROUP ON THE BASIS OF THE "SEVERITY" OF THE ILLNESS

AGE GROUP 30 - 44

SEVERITY:	0 + 1	2 + 3	TOTAL	% MILD
INOCULATED	3	8	11	27
UNINOCULATED	10	34	44	23
TOTAL:	13	42	55	

NOT SIGNIFICANT (FOURFOLD TABLE TEST)

4 (E)

COMPARISON OF PATIENTS INOCULATED WITH MIXED T.A.B. VACCINE WITH UNINOCULATED PATIENTS IN THE SAME AGE GROUP ON THE BASIS OF THE "SEVERITY" OF THE ILLNESS

AGE GROUP 30 - 44

SEVERITY:	0 + 1	2 + 3	TOTAL	% MILD
INOCULATED	1	3	4	25
UNINOCULATED	10	34	44	23
TOTAL:	11	37	48	

NOT SIGNIFICANT (FOURFOLD TABLE TEST)

I.A

LABORATORY FINDINGS IN 14 SYMPTOMLESS EXCRETERS AND 4 EXCRETERS WITH MINIMAL SYMPTOMS

Link No.	Age	Sex	Known Duration of Excretion (days)	Number of Positive Faeces	Known Ingestion Excretion Interval (days)	Maximum Temperature °F.	Date of Infection	Serum Agglutination Titres				Date of last T.A.B. Injection	Remarks
								Date	S.Typhi "H"	S.Typhi "O"	S.Typhi Vi.		
252	18/12	M	1	1		99.6	9.5.64	31.7.64	1: 25	1: 50		-	Rose spots.
517	7	M	22	2	19	99.0	16.5.64	1.6.64	-			1959	
								27.7.64	1: 50	-	1 : 5		
496	12	M	27	4		99.0	17.5.64	18.6.64	-			-	
								22.6.64	1: 25				
								27.7.64	1: 50	-	1 :20		
								10.2.65	1: 25	1: 25	1 :20		
450	14	F	1	1	32	98.2	17.5.64	13.6.64	-			-	Mild diarrhoea for 2 days
								22.6.64	-				
								3.7.64	-	-	1: 80		
								10.2.65	-	-	1: 40		
174	15	F	9	2		100.4		30.5.64	1:200			-	
								3.6.64	1:400+				
								27.6.64	1:100	-	1: 20		
								22.1.65	-	-	1: 10		
447	17	F	1	1	33	98.4	15.5.64	2.6.64	-			-	
								9.6.64	-				
								21.6.64	-				
								13.7.64	-	-	1: 10		
								28.1.65	-	-	1: 40		
243	18	M	1	1		99.9	23.5.64	8.6.64	1: 50			1949	
								13.11.64	1:200				
								10.7.64	1:100	-	1: 80	-	
								11.2.65	-	1: 50	1: 40		
484	25	M	6	2	53	98.4	9.5.64	27.5.64	1: 50			1962	Mild headache for 1 day
								2.6.64	1:100				
								21.6.64	1:100				
								5.7.64	1:100				
								1.8.64	1:200	1:100	1: 5		
								4.9.64	1:200	1:100	-		
446	26	F	1	1		98.2	16.5.64	18.6.64	-			1960	Pregnant; no weight gain for 1 week.
							23.5.64	26.6.64	-				
								4.7.64	-				
								26.7.64	1: 50	-	1: 40		
								10.2.65	-	1: 50	1: 40		
479	28	M	8	3	38	99.6	8.5.64	15.6.64	1: 25			-	
								20.7.64	1: 50	-	1: 5		
								24.2.65	1:100	-	1: 5		
459	30	M	1	1	23	98.4	9.5.64	29.5.64	1: 25			1953	
								10.6.64	1: 50				
								6.7.64	1:100	-	1: 10		
								11.2.65	1: 50	-	1: 5		
553	44	F	1	1		98.4	12.5.64	15.6.64	-			-	
								23.6.64	-				
								10.7.64	1: 25	-			
								15.7.64	-	-			
466	48	M	5	2	42	98.0	23.5.64	20.6.64	-			1942	
								27.6.64	1: 25				
								1.7.64	-				
								20.7.64	-	1: 50	1: 10		
								9.2.65	-	-	-		
507	49	M	8	3	43	99.2	9.5.64	9.6.64	1: 25			-	Mild headache for 2 days
								16.6.64	1: 25				
								25.6.64	1: 25				
								26.7.64	-	-	1: 10		
								10.2.65	-	-	1: 10		
18	53	F	4	2		98.8	8.5.64	29.5.64	1: 50			-	Mild diarrhoea for 2 days.
								1.6.64	1:100				
								27.6.64	-	-	1: 80		
								19.9.64	-	-	-		
470	54	M	8	3	43	98.2	8.5.64	2.6.64	-			1941	
								8.6.64	-				
								24.6.64	-				
								19.7.64	-	-	1: 5		
348	60	M	1	1	10	100.0	22.5.64	6.6.64	-			-	Blood culture positive 5 days after stool culture.
								11.6.64	-				
								30.6.64	-	-	1: 10		
								4.2.64	-	-	1: 5		
138	74	F	1	1	27	99.2	16.5.64	6.6.64	-			-	
								12.6.64	-	-			
								18.6.64	-	-			
								9.7.64	-	-	1: 10		
								14.10.64	-	-	-		

N.B. Serum agglutination: NIL result shown by hyphen, thus- -

Where no entry appears, the test was not done.

1.B

ASYMPTOMATIC EXCRETERS - SEX DISTRIBUTION

ASYMPTOMATIC		ALL PROVED TYPHOID PATIENTS	
MALES	FEMALES	MALES	FEMALES
11	7	182	287
61%	39%	39%	61%

I.A

DETAILS OF 35 PATIENTS WHO SHOWED NO ANTIBODY RESPONSE - ABERDEEN TYPHOID C

LINK No.	AGE	SEX	SEVERITY	INITIAL TREATMENT		DURATION OF ILLNESS BEFORE TREATMENT (DAYS)	DURATION OF PYREXIA ON TREATMENT (DAYS)	OTHER TREATMENT	DAY OF ILLNESS ON WHICH FIRST SPECIMEN TAKEN	NUMBER OF POSITIVE ISOLATIONS	
				ANTI-BIOTIC	DAILY DOSE MG/KG.					BLOOD	STOOL
469	2	M	1	AMP.	39	9	3		4	0	1
500	2	F	1	AMP.	66	7	0		3	0	1
327	6	M	1	CHLOR.	26	8	1	AMP.	4	1	3
150	7	M	1	CHLOR.	42	7	12		6	1	0
250	7	F	3	AMP.	34	3	7		1	0	0
502	8	M	3	CHLOR.	34	10	7	AMP.	7	3	1
485	9	F	3	CHLOR.	20	5	5	L.T. AMP.	1	1	4
324	10	M	3	AMP.	31	3	12		8	0	6
39	10	M	2	MIXED		5	3	L.T. AMP.	3	2	4
397	14	F	2	CHLOR.	36	3	6		2	0	0
450	14	F	0	NONE					0	0	1
290	17	F	1	CHLOR.	04	2	2		12	0	0*
447	17	F	0	AMP.	77	0	0		0	0	1
107	21	F	1	CHLOR.	38	9	2		4	0	1
118	21	M	3	CHLOR.	26	4	5		3	1	1
156	28	F	1	CHLOR.	24	7	1	AMP.	4	0	2
305	34	F	1	CHLOR.	29	12	1		2	1	0
314	35	F	3	CHLOR.	21	7	5	L.T. AMP.	7	2	2
463	36	F	2	CHLOR.	33	4	10		14	1	1
97	37	M	2	CHLOR.	44	2	6		4	0	0
67	37	F	3	CHLOR.	33	3	4	L.T. AMP.	3	1	4
23	42	F	2	CHLOR.	29	12	4		6	0	3
338	50	F	3	CHLOR.	24	7	4		2	1	2
43	51	M	0	NONE					0	1	0
350	52	M	2	CHLOR.	20	2	5		2	0	0*
470	54	M	0	CHLOR.	41	0	0		0	0	3
57	57	F	0	NONE					0	1	0
288	58	F	1	CHLOR.	31	3	3		3	0	0
205	59	F	2	CHLOR.	33	1	8		4	0	1
121	59	M	3	CHLOR.	24	6	3		3	1	0
134	60	F	3	CHLOR.	26	13	5	CHLOR.	6	1	2
480	60	M	3	CHLOR.	24	8	1		2	1	0
348	60	M	0	CHLOR.	19	0	6		0	1	2
161	63	F	1	CHLOR.	36	14	3		4	0	0
138	74	F	0	NONE					0	0	1

CHLOR. = CHLORAMPHENICOL. AMP. = AMPICILLIN. L.T.AMP. = "LONG TERM" AMPICILLIN.

* = POSITIVE URINE CULTURE.

I.B - Distribution of Relapses in Patients with No Antibody Response compared with those with "Normal" Antibody Response

Response	Relapse	No Relapse	Totals
No Antibody Response	1 (6)	34 (29)	35
Normal Response	57 (52)	238 (243)	295
Totals:	58	272	330

$\chi^2 = 4.77$ D.F. = 1 $P < 0.05$ possibly significant.

I.C - Distribution of "severity" of Initial Infection in Patients with No Antibody Response compared with those with "Normal" Antibody Response

Severity:	0 + 1	2 + 3	Totals
No Antibody Response	17 (8)	18 (27)	35
Normal Response	59 (68)	236 (227)	295
Totals:	76	254	330

$\chi^2 = 12.84$ D.F. = 1 $P < 0.00050$ - highly significant.

2.A

DETAILS OF 101 PATIENTS WHO SHOWED A MINIMAL ANTIBODY RESPONSE

LINK No.	AGE	SEX	SEVERITY OF ILLNESS	INITIAL TREATMENT		DURATION OF CLINICAL ILLNESS BEFORE TREATMENT (DAYS)	DURATION OF PYREXIA ON TREATMENT (DAYS)	SUBSEQUENT TREATMENT	POSITIVE ISOLATIONS		B.
				ANTIBIOTIC	DAILY DOSE MG/KG.				No. OF BLOOD SPECIMENS	No. OF FAECAL SPECIMENS	
331	2	F	3	AMP.	64	2	8		1	3	
323	2	F	3	AMP.	74	2	9		1	1	
12	2	M	3	CHLOR.	38	3	6	AMP.;L.T.AMP.	NIL	3	
187	3	F	3	MIXED		3	8		1	NIL	
333	4	M	3	AMP.	57	5	15	CHLOR.	2	5	
506	4	M	3	CHLOR.	43	18	5	L.T. AMP.	1	4	
525	5	M	3	CHLOR.	30	9	7		2	1	
326	5	M	3	AMP.	53	6	21	CHLOR.	2	4	
66	6	F	3	MIXED		4	6		NIL	NIL	R
71	6	M	1	NONE					NIL	NIL	R
321	6	F	3	MIXED		5	21	AMP.;L.T.AMP.	2	2	
73	6	F	3	AMP.	41	5	3		2	1	
98	6	F	3	CHLOR.	56	9	2		1	2	
504	6	F	1	AMP.	16	7	7		NIL	1	R
433	6	M	3	AMP.	54	15	8		1	2	
283	6	M	3	CHLOR.	43	4	6	AMP.	1	NIL	
536	7	M	0	NONE					NIL	NIL	
517	7	M	0	AMP.	34	0	1	AMP.	NIL	2	R
432	7	F	3	CHLOR.	32	8	0		2	NIL	
437	9	F	3	MIXED		3	7		2	NIL	
313	9	M	3	AMP.	36	1	9	AMP.	1	2	
429	9	F	2	CHLOR.	27	5	7		NIL	1	S
493	10	M	3	CHLOR.	19	6	7	AMP.;L.T.AMP.	3	4	R
276	11	F	3	CHLOR.	30	5	5	[illegible]AMP.	1	1	
514	12	M	3	CHLOR.	49	7	2	L.T. AMP.	1	5	
496	12	M	0	CHLOR.	50	0	1		NIL	4	
221	13	F	3	CHLOR.	32	7	4		2	1	
222	13	M	3	CHLOR.	27	2	5	AMP.	2	1	
170	14	F	2	CHLOR.	19	0	1	AMP.	NIL	2	F
230	14	F	2	CHLOR.	3	9	3	AMP. CHLOR.	NIL	1	
342	15	F	3	CHLOR.	29	2	4		2	NIL	
81	15	F	3	CHLOR.	40	2	5	CHLOR.;L.T.AMP.	1	2	
76	16	F	3	CHLOR.	44	7	3		1	NIL	
94	16	M	3	CHLOR.	41	10	2		1	NIL	
255	17	F	3	CHLOR.	33	4	5	AMP.	1	2	
136	17	F	3	CHLOR.	26	5	3		---	---	
372	17	F	2	CHLOR.	28	6	2	L.T. AMP.	NIL	1	F
248	19	F	3	CHLOR.	36	7	3	L.T. AMP.	1	2	
424	19	F	2	CHLOR.	27	8	4		1	NIL	
244	20	F	3	CHLOR.	32	8	6		1	NIL	
261	21	M	3	CHLOR.	29	9	5	CHLOR.	3	NIL	
204	22	F	3	CHLOR.	31	10	7	CHLOR;CHLORTET.	2	3	
214	24	F	3	CHLOR.	36	7	5		NIL	1	
481	24	F	1	CHLOR.	42	14	1		NIL	2	
5	25	M	1	NONE					NIL	1	
209	25	F	3	CHLOR.	30	10	6	AMP.	NIL	NIL	
219	26	F	3	CHLOR.	33	6	4		NIL	1	
479	28	M	0	CHLOR.	34	0	7		NIL	3	
446	28	F	0	CHLOR.	29	10	0		NIL	1	
489	29	F	3	CHLOR.	35	10	3	AMP;CHLOR;CHLOR-:TET.	1	2	
309/											

Link No.	Age	Sex	Severity of Illness	Initial Treatment		Duration of Clinical Illness before Treatment (days)	Duration of Pyrexia on Treatment	Subsequent Treatment	Positive Isolations	
				Anti-biotic	Daily Dose mg/Kg				No. of Blood Specimens	No. of Faecal Specimens
309	29	M	3	Chlor.	18	7	3	Amp.	2	2
202	32	F	2	Chlor.	36	6	0	Chlor; Amp; L.T. Amp.	Nil	4
443	32	M	2	Chlor.	27	24	3		Nil	2
127	33	F	3	Chlor.	28	6	3		2	3
181	33	F	3	Chlor.	28	5	5	Amp.	1	2
357	34	M	3	Chlor.	21	10	3	Amp.	Nil	Nil
104	34	F	1	Chlor.	33	1	0		Nil	Nil
508	37	F	3	Chlor.	24	2	4	Amp.	Nil	3
253	39	M	1	Chlor.	23	10	1		Nil	2
160	39	M	3	Chlor.	25	9	0	Amp.	Nil	4
19	41	F	3	Chlor.	26	1	7		2	Nil
139	42	M	1	Chlor.	19	7	2		Nil	1
426	43	F	3	Chlor.	28	7	13		2	Nil
182	43	M	2	Chlor.	31	4	5		Nil	1
185	44	F	2	Chlor.	28	7	5		Nil	1
195	44	M	2	Chlor.	28	2	3	Amp.	1	4
242	44	F	3	Chlor.	31	8	3	Chlor.	2	4
193	45	F	1	Chlor.	39	3	0	L.T. Amp.	2	Nil
169	45	F	3	Chlor.	35	8	2		Nil	1
280	46	F	3	Chlor.	60	8	4		1	Nil
196	47	F	2	Chlor.	30	12	5		Nil	1
249	47	F	1	Chlor.	29	8	4		Nil	Nil
439	47	F	3	Chlor.	48	6	5		1	1
466	47	M	0	None					Nil	2
490	47	M	3	Chlor.	27	14	3	Amp.	1	3
101	48	F	3	Chlor.	31	9	5		1	Nil
231	48	F	3	Chlor.	24	14	10		1	Nil
507	49	M	0	Chlor.	34	28	3		Nil	3
297	49	F	3	Chlor.	40	3	6		Nil	1
2	50	F	3	Chlor.	21	5	3	Amp.	1	1
494	53	F	1	Chlor.	30	28	1		Nil	3
370	53	M	2	Mixed		3	4	Amp.	Nil	1
247	53	F	2	Chlor.	28	14	8		Nil	2
387	55	M	3	None					Nil	Nil
405	55	F	2	Chlor.	26	12	2		1	Nil
473	57	M	1	Chlor.	32	3	0		Nil	1
28	58	F	1	Chlor.	29	6	2		Nil	Nil
130	59	F	2	Chlor.	26	6	17		Nil	1
296	61	F	1	Chlor.	27	10	0		Nil	Nil
302	63	F	3	Chlor.	42	8	6	L.T. Amp.	1	2
25	63	M	3	Chlor.	21	1	3		1	3
125	63	F	3	Chlor.	35	8	4	Amp.	1	1
472	63	M	3	Chlor.	26	14	3	Chlor.	Nil	2
88	64	F	3	Chlor.	31	5	3		1	2
294	64	F	1	Chlor.	31	3	1		1	Nil
401	65	F	3	Chlor.	43	15	4		2	1
353	66	F	3	Chlor.	30	0	6		1	Nil
93	71	M	2	Chlor.	29	7	2	Amp	Nil	1
99	73	F	3	Chlor.	38	16	5		1	Nil
9	74	F	3	Chlor.	39	9	14	Chlor.	2	1
179	75	F	3	Chlor.	21	8	3	L.T. Amp.	Nil	1

NOTE: Chlor. = Chloramphenicol; Amp. = Ampicillin
Chlortet. = Chlortetracycline. L.T.Amp. = "Long-term" Ampicillin.

3.A

DETAILS OF 28 PATIENTS WHO SHOWED A DELAYED ANTIBODY RESPON

ABERDEEN TYPHOID OUTBREAK, 1964

LINK No.	AGE	SEX	SEVERITY	INITIAL TREATMENT		DURATION OF ILLNESS BEFORE TREATMENT (DAYS)	DURATION OF PYREXIA ON TREATMENT (DAYS)	OTHER TREATMENT	S. TYPHI AGG			
									ADMISSION		DISCHARGE	
				ANTIBIOTIC	DAILY DOSE MG/KG.				'H'	'O'	'H'	'O'
31	3	M	3	CHLOR.	38	8	5	AMP.	1:25	-	1:25	NIL
518	3	M	3	AMP.		10	9	L.T.AMP	1:50	-	1:50	NIL
515	3	M	1	CHLOR.	22	5	0	AMP&L.T.AMP.	NIL	-	NIL	NIL
319	7	M	3	MIXED		4	9	L.T.AMP.	1:25	-	NIL	NIL
329	7	F	3	CHLOR.	39	12	8	L.T.AMP.	NIL	-	NIL	NIL
456	10	M	3	CHLOR.	22	9	3		NIL	-	NIL	NIL
375	14	F	2	NONE					NIL	-	NIL	NIL
225	16	F	3	CHLOR.	29	6	4	AMP.	1:25	NIL	1:25	1:25
272	16	F	3	CHLOR.	32	7	5	L.T.AMP.	NIL	NIL	NIL	NIL
289	18	F	3	CHLOR.	33	5	5	L.T.AMP.	1:100	-	1:25	1:50
224	19	F	3	CHLOR.	44	9	5		1:25	-	NIL	NIL
293	21	F	2	CHLOR.	21	6	3		1:25	-	1:25	NIL
84	22	F	3	CHLOR.	34	12	3	CHLOR.+ AMP.	NIL	-	NIL	NIL
123	24	F	0	NONE					NIL	-	NIL	NIL
468	25	F	2	CHLOR.	40	9	1		1:100	-	1:100	NIL
471	26	F	3	CHLOR.	31	1	5	AMP.	NIL	-	NIL	1:50
495	26	F	3	CHLOR.	39	15	3	AMP.	1:25	-	1:25	NIL
275	27	M	3	CHLOR.	24	3	4	AMP.	1:50	-	1:25	1:25
295	28	F	3	CHLOR.	42	6	4	METHAC.	NIL	-	NIL	NIL
530	29	M	3	CHLOR.	27	7	2	AMP. METHAC.	1:50	-	1:1600	NIL
83	30	F	3	CHLOR.	30	4	7	CHLOR.AMP. CEPHALOSP.	1:50	-	1:50	NIL
191	31	F	2	CHLOR.	17	7	5		1:50	-	1:50	NIL
72	34	F	3	CHLOR.	23	9	3	AMP.CHLOR. METHAC.	1:100	-	NIL	NIL
213	50	M	3	CHLOR.	30	14	6		1:100	-	1:100	NIL
475	54	F	3	CHLOR.	26	2	15		1:25	-	1:100	NIL
291	67	F	3	CHLOR.	19	7	8	AMP.METHAC.	NIL	-	1:200	NIL
340	82	F	3	CHLOR.	24	1	21		NIL	-	NIL	NIL
59	84	M	0	CHLOR.	30	0	0		1:50	-	1:50	NIL

CHLOR. = CHLORAMPHENICOL. AMP. = AMPICILLIN. L.T.AMP. = "LONG TERM" AMPICILLIN.

CEPHALOSP. = CEPHALOSPORIN.

3.B

Distribution of Single and Multiple Treatments between Patients with Delayed Antibody Response compared with those with "Normal" Antibody Response

Response	Single Treatment	Multiple Treatments	Total Treated
Delayed Antibody Response	9 (15)	17 (11)	26
No Response	172 (166)	119 (125)	291
Totals:	181	136	317

$\chi^2 = 4.88$ D.F. = 1 $P < 0.05$ - possibly significant.

4. DETAILS OF 295 PATIENTS WHO SHOWED A "NORMAL" ANTIBODY RESPONSE

No.	Age	Sex	Severity of Illness	Initial Treatment: Antibiotic	Initial Treatment: Daily Dose mg/Kg	Duration of Clinical Illness before Treatment (days)	Duration of Pyrexia on Treatment (days)	Subsequent Treatment	Levels of Agglutination Titres: Admission 'H'	Admission 'O'	Discharge 'H'	Discharge 'O'	3 Months 'H'	3 Months 'O'	6 Months 'H'	6 Months 'O'	Remarks
497	1	F	3	Amp.	86	5	14	Amp.	1:320	P.I:200+	1:25	1:100	-	-	-	-	Excreter
431	16/12	F	3	Chlor.	33	9	3		1:100	Nil	Nil	1:100	-	-	-	-	
505	16/12	M	3	Amp.	36	8	6		1:100	P.I:200+	1:50	Nil	Nil	Nil	-	-	Excreter
91	18/12	F	2	Chlor.	43	7	3		1:1600+	-	1:25	Nil	Nil	Nil	-	1:25	
307	18/12	M	2	Chlor.	50	5	4		1:100		Nil	Nil	Nil	Nil	Nil	Nil	
435	19/12	M	3	Amp.	36	14	15		1:25	P.I:200+	Nil	Nil	Nil	Nil	Nil	Nil	
521	2	M	3	Mixed		4	9	Amp.	-	P.I:200+	Nil	Nil	Nil	Nil	Nil	1:25	Excreter
328	2	M	1	Amp.	65	7	7		1:100	Nil;P.I:320	1:25	Nil	-	-	-	-	
527	2	M	3	Mixed		9	6		1:50	Nil	1:50	1:100	1:50	Nil	-	-	
510	2	F	1	Chlor.	32	6	2	Amp.	1:100	-	1:25	Nil	Nil	Nil	-	-	Excreter
49	3	F	2	Chlor.	41	4	7	Amp.	1:600+	1:400	1:100	Nil	1:50	Nil	1:25	1:50	Excreter
112	4	F	3	Mixed		5	4		1:400+	-	1:25	Nil	1:25	1:100	Nil	Nil	
516	4	M	3	Chlor.	25	4	5	L.T. Amp.	1:100	-	1:100	1:50	1:50	Nil	1:50	1:50	Excreter
511	4	F	2	Amp.	49	8	14		Nil	-	Nil	1:20	Nil	Nil	-	-	Excreter
310	4	M	3	Mixed		4	5		1:400+	-	1:25	Nil	Nil	Nil	Nil	1:50	Excreter
332	5	M	3	Mixed		2	11	Amp.;L.T.Amp.	1:100	-	1:50	Nil	Nil	Nil	1:25	1:50	Excreter
522	5	F	3	Chlor.	32	6	4	Amp.	1:200	-	1:100	Nil	1:100	Nil	1:50	1:200	Relapsed;excreter
519	6	M	1	Amp.	37	19	1	Amp.	1:400+	-	1:50	1:50	1:50	Nil	-	-	Excreter
322	6	F	3	Chlor.	45	14	6		1:100	P.I:200+	Nil	Nil	Nil	Nil	Nil	Nil	Excreter
220	6	F	3	Chlor.	38	9	4		1:100	-	Nil	Nil	1:50	1:25	1:25	Nil	
434	6	F	3	Chlor.	24	9	6		1:200	-	Nil	Nil	1:25	Nil	Nil	Nil	
526	6	F	3	Amp.	37	7	15	Amp.	1:100	-	Nil	Nil	Nil	Nil	-	-	Excreter
438	6	F	3	Amp.	41	3	2		1:25	Nil;P.I:200+	Nil	1:25	Nil	Nil	-	-	
27	7	M	3	Mixed		2	7	Amp.	1:200	-	Nil	Nil	Nil	Nil	1:25	Nil	Excreter
512	7	M	3	Mixed		9	5		1:100	-	1:400	Nil	1:50	Nil	-	-	Relapsed
520	7	F	3	Chlor.	30	6	6	Amp.	1:50	-	1:100	1:100	1:25	1:25	Nil	Nil	
278	7	F	2	Chlor.	44	4	3	Amp.	1:1600+	1:50	1:50	1:50	1:50	1:100	1:50	1:100	Excreter
69	8	M	2	Mixed		11	2	L.T. Amp.	1:25	-	1:400	1:50	1:50	Nil	1:25	Nil	Relapsed;excreter
64	8	F	2	Mixed		5	3	L.T. Amp.	1:200	-	Nil	Nil	Nil	Nil	Nil	Nil	Excreter
284	8	F	2	Mixed		10	3	Amp.	1:400+	-	1:25	Nil	Nil	Nil	1:25	Nil	Excreter
151	8	F	2	Chlor.	36	1	2	Amp.;L.T. Amp.	Nil	-	1:400	Nil	Nil	Nil	Nil	Nil	Relapsed;excreter
320	9	M	3	Chlor.	21	5	4	L.T. Amp.	1:400	-	1:50	1:50	Nil	Nil	Nil	1:25	Excreter
430	9	F	3	Chlor.	35	15	7		1:400+	-	1:100	-	1:25	Nil	-	-	
534	9	F	3	Chlor.	36	30	2		1:25	Nil;P.I:320	1:50	Nil	Nil	Nil	Nil	Nil	
241	9	F	3	Mixed		5	10	Amp.;L.T.Amp.	1:100	-	1:100	Nil	1:25	Nil	1:25	Nil	Relapsed
52	10	F	3	Chlor.	27	6	11		1:1600+	1:800	1:50	1:50	1:100	Nil	1:25	Nil	Excreter
400	10	M	3	Amp.	29	4	11		1:50	Nil;P.I:320	Nil	Nil	Nil	Nil	Nil	Nil	
234	10	F	3	Amp.	28	10	7		1:400+	-	1:400	Nil	1:100	Nil	-	-	Excreter
251	10	M	3	Mixed		7	4		1:400	-	1:50	Nil	-	-	-	-	
503	10	M	3	Mixed		7	21	L.T. Amp.	1:25	Nil;P.I:200+	1:50	Nil	Nil	1:100	-	-	Excreter
271	10	M	3	Chlor.	20	1	6		1:100	-	1:100	Nil	Nil	Nil	1:25	Nil	
173	11	M	3	Mixed		5	13		1:400+	-	Nil	Nil	Nil	Nil	Nil	Nil	
192	11	F	3	Chlor.	36	6	3		1:200	-	1:50	Nil	Nil	Nil	Nil	Nil	Excreter
300	11	F	3	Mixed		6	12		1:25	-	1:100	Nil	Nil	Nil	1:25	1:50	Excreter
63	11	F	1	Chlor.	22	9	2	Amp.	1:50	-	1:100	Nil	Nil	Nil	Nil	Nil	Relapsed
172	11	M	3	Chlor.	40	5	7		1:1600	Nil;P.I:100	1:200	Nil	Nil	Nil	1:25	Nil	
30	12	F	3	Mixed		8	3		1:400	-	1:800	Nil	1:25	Nil	1:50	Nil	
38	12	M	2	Chlor.	26	5	3	L.T. Amp.	1:25	-	1:100	Nil	Nil	Nil	1:25	Nil	Excreter
419	12	M	2	Chlor.	29	4	5		1:25	Nil;P.I:200+	1:25	Nil	1:25	Nil	1:25	Nil	
274	12	F	3	Chlor.	29	4	2	Methac;Amp;Chlor.	1:50	-	1:100	Nil	1:50	Nil	1:25	1:100	Relapsed;excreter
7	13	F	3	Chlor.	36	2	5	Chlor.	1:100	-	1:100	Nil	1:50	Nil	Nil	Nil	Relapses
339	13	M	3	Chlor.	41	8	3		Nil	Nil;P.I:100	Nil	1:50	Nil	Nil	Nil	1:25	
175	13	F	2	Chlor.	8	4	1		1:400+	-	1:100	Nil	1:1600	Nil	1:200	1:200	
203	13	F	3	Chlor.	42	6	4	Chlor.	1:400	Nil	1:200	1:25	1:25	Nil	Nil	1:25	Relapsed;excreter
40	14	M	2	Chlor.	36	3	5		Nil	-	1:100	-	Nil	Nil	Nil	Nil	Excreter
131	14	F	1	Chlor.	29	5	15		1:100	-	1:50	1:50	-	-	-	-	
152	14	M	3	Chlor.	26	3	4		1:50	Nil;P.I:100	Nil	Nil	Nil	Nil	Nil	Nil	
417	14	M	3	Chlor.	27	11	4		1:800	P.I:100	1:25	Nil	Nil	Nil	1:25	1:25	
365	14	F	3	Chlor.	33	4	4		1:100	P.I:100	Nil	Nil	Nil	Nil	-	-	
45	15	F	3	Chlor.	35	7	3	Amp;Chlor;Chlortet.	1:25	-	1:100	Nil	1:25	Nil	Nil	1:25	Relapsed.
133	15	F	3	Chlor.	34	7	12	Chlor.	1:400+	-	1:50	Nil	Nil	Nil	-	-	Relapsed
174	15	F	2	Chlor.	34	0	7		1:200	-	1:100	Nil	Nil	Nil	Nil	Nil	
460	15	M	1	Amp.	49	22	1		1:400+	-	1:100	Nil	Nil	Nil	Nil	Nil	
16	16	F	3	Chlor.	31	5	5		1:200	-	1:25	Nil	Nil	Nil	-	-	Excreter

4. DETAILS OF 295 PATIENTS WHO SHOWED A "NORMAL" ANTIBODY RESPONSE (CONTD.) - PAGE 2

No.	Age	Sex	Severity of Illness	Initial Treatment: Antibiotic	Initial Treatment: Daily Dose mg/Kg	Duration of Clinical Illness before Treatment (days)	Duration of Pyrexia on Treatment (days)	Subsequent Treatment	Levels of Agglutination Titres: Admission "H"	Admission "O"	Discharge "H"	Discharge "O"	3 months "H"	3 months "O"	6 months "H"	6 months "O"	Remarks
87	16	F	3	CHLOR.	34	6	4		1:400	NIL;P.1:200+	-	-	NIL	1:50	NIL	NIL	
103	16	M	3	CHLOR.	41	8	6		1:50	-	NIL	1:100	NIL	NIL	NIL	NIL	EXCRETER
153	16	F	2	CHLOR.	30	4	4		1:100	-	NIL	NIL	NIL	NIL	NIL	1:50	
165	16	F	3	CHLOR.	25	3	4		1:100	-	1:50	NIL	NIL	NIL	NIL	NIL	
258	16	F	3	CHLOR.	29	7	2		1:25	-	1:100	NIL	1:50	NIL	1:25	1:25	
260	16	F	3	CHLOR.	22	7	5		1:25	NIL;P.1:200+	NIL	NIL	NIL	NIL	NIL	1:100	
341	17	F	3	CHLOR.	26	9	4		1:25	NIL;P.1:200+	NIL	NIL	-	-	-	-	INOCULATED 1961
65	17	F	3	CHLOR.	28	13	3		1:200	-	1:50	NIL	1:25	1:200	NIL	NIL	
77	17	F	3	CHLOR.	29	14	4		1:250	NIL; 1:200+	1:200	1:50	1:100	NIL	1:100	NIL	
413	17	F	3	CHLOR.	24	9	7		1:25	NIL;P.1:100	1:50	NIL	1:25	NIL	1:25	NIL	INOCULATED 1962
197	17	F	3	CHLOR.	24	7	9		1:200	-	NIL	NIL	NIL	NIL	NIL	1:200	
201	17	F	2	CHLOR.	42	8	4	AMP.	1:100	NIL;P.1:100	1:50	NIL	1:25	NIL	-	-	EXCRETER
208	17	F	3	CHLOR.	36	2	5	AMP.	1:200	-	1:25	NIL	NIL	NIL	NIL	NIL	EXCRETER
257	17	F	3	CHLOR.	36	0	7	AMP.; L.T. AMP.	1:1600	-	1:800	NIL	1:400	NIL	1:200	1:400	EXCRETER
483	17	F	2	CHLOR.	32	13	2		1:100	-	1:25	NIL	NIL	NIL	NIL	NIL	EXCRETER
26	18	M	3	CHLOR.	21	6	5	AMP. METHAC.	1:400	-	1:100	NIL	-	-	-	-	EXCRETER
408	18	F	1	CHLOR.	26	21	2		1:1280	NIL;P.1:200+	1:100	NIL	1:25	NIL	NIL	NIL	
96	18	F	3	CHLOR.	44	7	4		1:1600	-	1:50	NIL	NIL	NIL	NIL	NIL	RELAPSED
418	18	F	3	CHLOR.	29	0	6		1:400	P.1:200+	1:200	NIL	1:100	NIL	1:100	1:100	
171	18	M	3	CHLOR.	42	9	4		1:1600+	-	1:200	NIL	NIL	NIL	1:25	NIL	
498	18	M	3	CHLOR.	21	6	6	AMP. L.T.AMP.	1:50	-	NIL	1:100	NIL	NIL	NIL	NIL	EXCRETER
210	16	F	3	CHLOR.	24	5	3	L.T.AMP.	1:400+	-	1:100	NIL	NIL	NIL	-	1:400	EXCRETER
246	18	F	2	CHLOR.	22	3	5		1:25	NIL.P.1:50	1:100	NIL	NIL	NIL	NIL	NIL	
243	18	M	1	CHLOR.	24	1	3		1:200	-	1:100	NIL	NIL	NIL	NIL	1:50	INOCULATED
292	18	F	3	CHLOR.	34	9	9		1:5120	NIL	1:400	NIL	1:50	NIL	NIL	NIL	
464	18	M	3	CHLOR.	40	6	4		1:50	-	1:25	NIL	NIL	NIL	NIL	1:100	
137	19	F	3	CHLOR.	26	5	4		1:200	-	1:25	NIL	1:25	NIL	1:25	NIL	EXCRETER
354	19	F	3	CHLOR.	24	1	3	L.T. AMP.	NIL	P.1:100	1:50	NIL	1:25	NIL	1:25	NIL	EXCRETER
267	19	F	3	CHLOR.	38	7	3		1:2560	NIL P.1:320	1:1600	NIL	NIL	NIL	NIL	NIL	
21	19	F	3	CHLOR.	29	8	4	L.T. AMP.	1:25	-	1:100	NIL	1:50	NIL	1:25	1:25	EXCRETER
232	19	M	3	CHLOR.	31	14	2		1:400+	-	1:100	NIL	1:50	NIL	NIL	NIL	
414	20	M	3	CHLOR.	24	9	4	AMP.	1:100	NIL	NIL	NIL	1:25	NIL	-	-	RELAPSED
343	20	M	3	CHLOR.	26	4	4	AMP.	1:50	NIL.P.1:100	NIL	NIL	NIL	NIL	NIL	1:50	RELAPSED
416	20	M	3	CHLOR.	25	5	3		1:200	-	NIL	NIL	NIL	NIL	NIL	NIL	
62	20	F	3	CHLOR.	40	7	3		1:1280	NIL.P.1:200+	1:200	NIL	NIL	NIL	NIL	1:50	
70	20	F	1	CHLOR.	32	6	1		1:50	-	1:100	-	1:100	1:25	1:25	-	INOCULATED
427	20	F	3	CHLOR.	28	5	3		1:50	P.1:200	1:100	NIL	NIL	NIL	-	-	
337	21	M	3	CHLOR.	22	8	4		1:25	P.1:200+	NIL	NIL	NIL	NIL	-	-	
85	21	M	3	CHLOR.	32	8	4		1:100	-	-	-	NIL	NIL	NIL	NIL	
108	21	M	3	CHLOR.	30	7	3		1:100	-	1:50	NIL	1:100	1:25	1:25	1:25	EXCRETER
157	21	M	3	CHLOR.	34	14	2		1:400	-	1:50	-	1:100	1:50	1:25	1:50	
3	21	F	3	CHLOR.	30	11	3	AMP.	1:400+	-	1:25	NIL	NIL	NIL	NIL	NIL	EXCRETER
78	21	F	3	CHLOR.	29	9	5	AMP.	1:25	-	1:400	NIL	1:25	NIL	1:50	NIL	EXCRETER
539	21	F	3	MIXED.		18	8		1:240	NIL	1:120	NIL	1:25	NIL	-	-	INOCULATED 1964
335	22	M	3	CHLOR.	22	6	3		1:100	P.1:200+	1:50	NIL	-	-	NIL	NIL	
336	22	F	2	CHLOR.	26	14	1		1:400	P.1:100	1:25	NIL	1:25	NIL	NIL	NIL	EXCRETER
189	22	F	3	CHLOR.	35	3	3		1:800	-	1:100	NIL	NIL	NIL	NIL	NIL	
263	22	F	3	CHLOR.	25	14	4		1:200	-	NIL	NIL	1:25	1:50	NIL	1:50	
406	23	M	2	CHLOR.	19	6	4		1:25	P.1:100	NIL	NIL	NIL	NIL	NIL	NIL	
109	23	F	3	CHLOR.	41	8	4		NIL	-	1:50	1:400	-	1:200	-	1:400	
411	24	M	3	CHLOR.	16	14	8		1:200	NIL;P.1:200+	1:25	NIL	NIL	NIL	NIL	NIL	
90	24	M	1	CHLOR.	33	7	5		1:1600+	-	1:200	NIL	NIL	NIL	NIL	NIL	EXCRETER
449	24	M	1	CHLOR.	29	9	3		1:1000	P.1:200+	1:200	-	-	-	-	-	INOCULATED
371	24	F	2	MIXED		9	3	L.T. AMP.	1:1600+	-	1:100	NIL	1:25	NIL	-	-	EXCRETER
478	24	F	2	CHLOR.	29	10	2	AMP.	1:200	-	1:200	NIL	1:400	NIL	1:25	NIL	EXCRETER
268	24	F	3	CHLOR.	24	4	4	L.T. AMP.	1:100	-	1:50	NIL	-	-	NIL	NIL	EXCRETER
484	25	M	1	AMP.	59	54	0		1:100	-	1:200	1:100	1:200	1:100	-	-	INOCULATED
236	25	M	3	CHLOR.	39	8	5	AMP.	1:1600+	-	-	-	1:25	NIL			RELAPSED
144	26	M	2	CHLOR.	21	8	4		1:25	-	-	1:100	NIL	NIL	NIL	1:100	EXCRETER
422	26	M	3	CHLOR.	25	4	4	L.T. AMP.	1:25	P.NIL	1:100	NIL	1:25	NIL	1:25	NIL	EXCRETER;RELAPSED
199/																	

4. DETAILS OF 295 PATIENTS WHO SHOWED A "NORMAL" ANTIBODY RESPONSE (CONTD.) - PAGE 3

No.	Age	Sex	Severity of Illness	Initial Treatment: Anti-biotic	Initial Treatment: Daily Dose mg/Kg.	Duration of Clinical Illness before Treatment (days)	Duration of Pyrexia on Treatment (days)	Subsequent Treatment	Levels of Agglutination Titres: Admission 'H'	Admission 'O'	Discharge 'H'	Discharge 'O'	3 Months 'H'	3 Months 'O'	6 Months 'H'	6 Months 'O'	Remarks
159	26	F	3	Chlor.	34	8	2		1:200	-	1:50	NIL	NIL	NIL	NIL	NIL	
190	26	F	3	Chlor.	32	5	9	Amp., Chlor; Chlor.	NIL	-	1:80	NIL	1:200	-	1:100	1:100	Excreter; Relapsed
215	26	F	3	Chlor.	38	3	4	Chlor.	1:100	-	1:25	NIL	1:50	NIL	NIL	NIL	Relapsed
254	26	F	3	Chlor.	24	12	3		1:100	-	1:25	NIL	NIL	NIL	0	-	
412	27	M	1	Chlor.	24	1	14		1:400	NIL	1:400	-	1:400	0	-	-	Inoculated
143	27	F	2	Chlor.	27	8	4		1:100	-	1:25	NIL	NIL	NIL	NIL	NIL	
186	27	F	3	Chlor.	30	3	5	Amp.	1:200	-	1:50	NIL	NIL	NIL	1:200	NIL	Excreter
32	28	M	2	Chlor.	24	5	5	L.T. Amp.	1:100	-	1:50	NIL	1:100	NIL	1:25	NIL	Excreter; Inoculated
378	28	M	1	Chlor.	22	8	1		1:200	-	1:800	NIL	1:800	-	1:400	-	
392	28	M	0	None		8			1:400	-	1:600	-	-	-	-	-	Inoculated
407	28	F	3	Chlor.	25	14	3	Amp; Chlor; Chlortet.	1:25	NIL	1:200	1:50	1:50	NIL	NIL	1:25	Relapsed
14	28	F	3	Chlor.	37	3	2		1:100	-	1:25	NIL	NIL	NIL	NIL	NIL	
34	28	F	3	Mixed		5	3	Amp.	1:100	-	1:25	NIL	1:25	NIL	-	-	Excreter
92	28	F	3	Chlor.	24	5	3	Amp.	1:400	-	1:200	NIL	1:200	NIL	1:50	NIL	Excreter; Inoculated.
102	28	F	2	Chlor.	26	2	10	L.T. Amp.	1:50	-	1:100	NIL	NIL	NIL	NIL	NIL	Excreter
356	28	F	3	Mixed		21	8		1:25	P.1:200+	NIL	NIL	NIL	NIL	-	-	
308	28	F	1	Chlor.	31	9	0		1:400+	-	1:200	NIL	1:25	NIL	1:25	NIL	Excreter
318	28	F	3	Chlor.	24	3	4		1:200	NIL; P.1:640+	1:200	-	-	-	1:200	1:100	Inoculated
312	29	M	3	Chlor.	25	2	6	Amp.	NIL	-	1:100	NIL	1:25	NIL	NIL	NIL	Relapsed
273	29	M	1	Chlor.	21	5	1	Amp.	1:25	NIL	1:100	NIL	1:100	NIL	1:100	NIL	Inoculated; Relapsed.
459	30	M	0	Chlor.	21	0	0		1:50	NIL	1:100	NIL	1:100	NIL	1:50	NIL	Inoculated
176	30	F	3	Chlor.	26	13	4	Chlor; Chlortet; L.T. Amp.	1:100	-	1:50	NIL	1:25	NIL	NIL	NIL	Excreter; Relapsed
51	31	M	3	Mixed		7	17		1:1600+	1:400	1:400	NIL	1:400	1:50	1:100	NIL	Inoculated
442	31	M	3	Chlor.	31	9	11	Amp.	1:200	-	1:25	NIL	NIL	NIL	NIL	NIL	Relapsed
68	31	M	1	Chlor.	22	3	1		1:200	-	1:200	-	1:200	-	-	-	Inoculated
216	31	M	1	Chlor.	29	3	1		1:200	-	NIL	NIL	NIL	NIL	NIL	NIL	
33	31	F	1	Chlor.	25	15	1		1:200	-	1:800	NIL	1:50	NIL	1:50	1:25	Excreter
306	31	F	3	Chlor.	37	12	4	Chlor.	1:100	-	1:25	NIL	1:25	1:100	NIL	1:200	Inoculated; Relapsed
22	32	M	3	Chlor.	20	10	8	Amp.	NIL	-	1:6400	NIL	1:800	-	1:100	NIL	Excreter; Relapsed
445	32	M	1	None					1:500	NIL; P.1:25	1:100	-	1:200	-	-	-	Inoculated
167	32	M	2	Chlor.	28	3	3		NIL	-	1:400	NIL	1:800	-	-	-	Inoculated
486	32	F	3	Chlor.	34	8	5	Amp. L.T. Amp.	1:200	-	1:200	NIL	1:50	NIL	NIL	NIL	Excreter; Relapsed
148	32	F	3	Chlor.	34	7	6	L.T. Amp.	1:200	-	1:100	NIL	1:50	-	1:25	NIL	Excreter
128	32	M	3	Chlor.	23	8	2	L.T. Amp.	1:100	-	1:100	NIL	1:50	-	1:25	NIL	Inoculated; Excreter
29	33	F	1	Chlor.	31	10	1	Amp.	1:200	-	1:25	NIL	1:25	1:50	1:25	1:100	Excreter
50	33	F	3	Chlor.	38	7	11	L.T. Amp.	1:6400+	1:3200+	1:800	NIL	1:800	NIL	1:50	1:50	Excreter
149	35	M	3	Chlor.	26	0	6		1:400+	-	1:200	NIL	1:50	NIL	1:25	NIL	Excreter; Inoculated
317	35	F	3	Chlor.	35	7	6		1:200	-	1:100	NIL	NIL	NIL	1:25	NIL	
277	36	M	3	Chlor.	29	13	2		1:200	-	1:50	NIL	NIL	NIL	1:25	NIL	
363	36	M	2	Chlor.	20	7	1		1:100	NIL	1:25	NIL	1:50	NIL	1:25	NIL	Inoculated
367	36	M	3	Chlor.	19	8	6	Chlor; Chlortet.	1:50	P.1:100	1:25	NIL	NIL	1:50	NIL	1:100	Inoculated; Relapsed
100	36	F	3	Chlor.	29	4	3	Amp.	NIL	-	1:100	NIL	1:25	-	-	-	Excreter
75	37	M	3	Chlor.	28	5	3	Amp.	1:1000	NIL; P.1:100	-	-	1:100	-	-	1:50	Inoculated; Relapsed
283	37	M	3	Chlor.	25	9	4		1:200	1:25	1:25	NIL	NIL	NIL	NIL	NIL	Inoculated
184	37	F	3	Chlor.	40	0	5	Chlor; L.T. Amp.	1:200	NIL	1:100	NIL	NIL	NIL	NIL	1:100	Excreter; Relapsed
194	37	F	1	Chlor.	42	0	3	Amp.	1:200	-	NIL	NIL	NIL	NIL	NIL	NIL	Excreter
223	37	F	3	Chlor.	24	6	8		1:100	P.1:100	1:25	NIL	NIL	NIL	-	-	
37	38	F	3	Chlor.	32	6	0		1:100	-	1:200	-	-	1:50	NIL	NIL	
509	38	F	3	Chlor.	25	2	3	Chlor. Chlortet; Amp.	NIL	-	1:25	1:100	-	-	-	-	Excreter; Relapsed
513	39	M	2	Chlor.	21	14	3	L.T. Amp.	1:50	NIL; P.1:100	NIL	NIL	NIL	NIL	NIL	NIL	Excreter
474	39	F	2	Chlor.	31	6	3	Chlor.	1:400	NIL	1:200	1:100	NIL	NIL	1:50	NIL	Relapsed
183	39	F	1	Chlor.	30	0	0	Amp.	1:400	NIL; P.1:100	1:400	[illegible]	1:200	-	-	-	Excreter
199	40	M	1	None					1:400+	-	1:400	-	1:800	-	1:400	-	Inoculated
347	40	M	3	Chlor.	24	0	4		1:100	P.1:200+	1:25	1:50	1:50	1:50	-	1:50	Inoculated
299	42	M	1	Chlor.	21	2	3		1:400	-	1:800	-	1:1600	-	1:800	-	Inoculated
455	43	M	3	Chlor.	34	7	8	Amp.	1:25	-	1:600	-	1:800	-	1:400	1:50	Inoculated; Relapsed
476	43	M	1	Chlor.	29	0	0		1:100	NIL	1:50	NIL	1:100	NIL	1:50	1:50	Inoculated
451	44	M	1	None					1:25	P.1:50	1:100	-	1:100	-	-	-	Inoculated
145	44	M	1	Chlor.	20	10	4		1:800	-	1:200	-	1:800	-	1:800	-	Inoculated

6/

4. DETAILS OF 295 PATIENTS WHO SHOWED A "NORMAL" ANTIBODY RESPONSE (CONTD.) - PAGE 4

No.	Age	Sex	Severity of Illness	Initial Treatment: Anti-biotic	Initial Treatment: Daily Dose mg/Kg	Duration of Clinical Illness before Treatment (days)	Duration of Pyrexia on Treatment (days)	Subsequent Treatment	Levels of Agglutination Titres: Admission 'H'	Admission 'O'	Discharge 'H'	Discharge 'O'	3 Months 'H'	3 Months 'O'	6 Months 'H'	6 Months 'O'	Remarks
6	43	F	3	Chlor.	33	5	10	Chlor. Amp.	1:1600	Nil;P.1:50	1:50	Nil	1:100	Nil	1:25	Nil	Relapsed
126	43	F	1	Chlor.	28	9	5		Nil	-	1:200	-	1:50	-	1:25	1:25	Inoculated
362	43	F	1	Chlor.	21	7	2	Amp.	1:25	Nil	1:100	Nil	1:50	Nil	1:25	Nil	Excreter
146	44	M	1	Chlor.	30	2	1		1:400+	-	1:400	-	1:400	-	1:400	-	Inoculated
352	44	M	3	Chlor.	19	10	4		1:100	-	1:200	-	1:100	-	1:25	1:100	Inoculated
376	44	M	1	None					1:25	-	1:200	Nil	1:200	Nil	1:200	Nil	Inoculated
13	44	F	3	Chlor.	37	4	0	Chlor. Amp. L.T. Amp.	1:200	-	1:25	Nil	Nil	Nil	Nil	Nil	Excreter; relapsed; inoculated.
217	44	M	1	Chlor.	26	2	2		1:200	-	1:100	Nil	1:100	Nil	1:200	1:50	Inoculated.
528	45	M	3	Chlor.	26	3	1		1:50	-	1:100	-	1:100	-	1:50	-	Inoculated
461	45	M	2	Chlor.	19	14	4	L.T. Amp.	1:100	P. Nil.	1:50	-	1:100	-	1:50	1:50	Excreter; inoculated
35	45	F	3	Chlor.	34	6	9	Chlor; Chlortet. Amp.	1:200	-	1:200	Nil	Nil	Nil	Nil	Nil	Relapsed
452	45	F	3	Chlor.	29	8	4		1:100	Nil;P.1:25	1:25	Nil	Nil	Nil	Nil	Nil	Inoculated
531	46	F	1	Chlor.	28	31	5	Amp. L.T. Amp. Amp. Methac	1:320	Nil	1:200	Nil	1:400	Nil	1:100	Nil	Carrier
465	47	F	3	Chlor.	29	8	10	Amp.	1:100	P.1:100	1:50	Nil	1:100	Nil	1:50	1:50	
369	47	F	1	Chlor.	29	10	2		1:400+	-	1:50	Nil	Nil	Nil	Nil	1:100	
344	47	M	2	Chlor.	24	8	5		1:200	Nil	1:100	Nil	1:400	-	1:100	Nil	Inoculated
60	48	F	3	Mixed		7	2	L.T. Amp.	Nil	-	1:400	1:100	1:200	Nil	1:50	Nil	Excreter
74	48	F	3	Chlor.	43	7	5	Amp., L.T. Amp.	Nil	-	1:400	1:50	1:100	-	1:50	-	Excreter
116	48	F	3	Chlor.	34	4	4		1:100	-	1:1600	0	1:200	1:100	1:200	1:200	Inoculated
499	48	F	1	Chlor.	19	0	4		1:50	Nil	1:200	Nil	1:100	Nil	1:100	Nil	Inoculated
304	48	F	3	Chlor.	26	3	12		1:320	Nil	Nil	Nil	Nil	Nil	-	-	
42	49	F	3	Mixed		0	3		1:25	-	1:50	Nil	1:50	Nil	1:25	Nil	
82	49	F	3	Chlor.	32	14	5		1:200	-	Nil	Nil	Nil	Nil	-	-	
265	49	F	3	Chlor.	26	7	6		1:200	Nil;P.1:160	1:800	1:25	1:800	-	1:1600	1:100	Inoculated 1941; excreter.
166	49	M	1	Chlor.	25	15	7		1:100	-	1:25	Nil	Nil	Nil	Nil	Nil	
550	49	M	1	Chlor.	22	18	3		1:100	P. Nil.	1:50	Nil	-	-	-	-	Inoculated
315	49	M	2	Chlor.	26	17	5		1:200	-	1:50	Nil	1:25	Nil	Nil	Nil	Inoculated
24	49	F	3	Chlor.	25	7	7	Amp.	1:1600+	-	1:800	-	-	-	-	-	Excreter
349	50	F	3	Chlor.	23	5	3		1:1000	Nil	1:50	Nil	Nil	Nil	1:25	Nil	
180	50	F	2	Chlor.	20	0	2		1:50	P. Nil.	-	1:100	Nil	Nil	Nil	1:50	Excreter
456	50	F	2	Chlor.	20	8	3	Amp.	1:800	-	1:100	Nil	1:25	Nil	Nil	1:50	Excreter; relapsed
256	50	F	1	Chlor.	30	6	5		1:1600+	-	1:400	Nil	1:50	Nil	1:50	Nil	
402	51	M	1	Chlor.	19	10	0		1:800	-	1:50	Nil	1:25	1:50	Nil	Nil	Excreter
115	51	F	2	Chlor.	27	28	18		1:400	-	1:3200+	Nil	1:12800	Nil	1:800	Nil	
227	52	F	3	Chlor.	25	14	4		1:100	-	Nil	Nil	Nil	Nil	Nil	1:25	
259	52	F	3	Chlor.	33	7	6		1:200	-	1:400	Nil	1:50	Nil	Nil	Nil	
113	53	M	2	Chlor.	29	10	8	Amp; Methac; L.T. Amp.	1:25	-	-	-	1:3200	1:50	1:3200	-	Carrier; inoculated
366	53	M	3	Chlor.	22	9	3		1:50	P.1:25	1:100	Nil	-	-	-	-	
364	53	M.	2	Chlor.	22	14	3		1:25	P.1:100	Nil	Nil	1:25	Nil	Nil	Nil	
18	53	F	0	Chlor.	39	16	0		1:200	-	Nil	Nil	Nil	Nil	Nil	Nil	
122	54	F	3	Chlor.	26	0	6	Chlor. Chlortet; LT Amp	1:25	-	1:200	Nil	1:50	Nil	Nil	Nil	Excreter; relapsed
11	54	M	2	Chlor.	23	13	3		1:400+	-	1:400	Nil	-	-	-	-	Inoculated
269	55	M	3	Chlor.	26	5	2	Amp.	1:100	-	Nil	Nil	Nil	Nil	Nil	Nil	Excreter
467	55	F	2	Chlor.	53	7	4	Chlor; Chlortet; Amp.	1:1600+	-	1:12800	Nil	1:1600	Nil	1:800	Nil	Excreter
164	55	F	2	Chlor.	23	26	4		1:25	P.1:200+	Nil	Nil	Nil	Nil	Nil	Nil	
421	55	F	1	Chlor.	31	8	1		1:400	P.1:100	Nil	Nil	1:50	1:25	-	-	
270	55	F	3	Chlor.	24	6	11	Chlor; Chlortet	Nil	-	1:1600	-	1:400	Nil	1:100	Nil	Relapsed
285	55	F	3	Chlor.	24	5	4	Amp.	1:100	1:25	1:200	Nil	1:400	Nil	-	-	Excreter
17	56	M	3	Chlor.	24	8	3	Chlor.; L.T. Amp.	1:100	-	1:400	1:50	1:100	1:25	1:50	-	Excreter; inoculated; relapsed
8	56	F	3	Chlor.	34	7	27	Chlor; Amp; Methac	1:100	-	1:3200	Nil	1:200	Nil	1:50	Nil	Excreter; relapsed
95	56	F	3	Mixed		7	17	Amp. Chlor.	1:200	-	1:25	-	Nil	Nil	Nil	Nil	Relapsed
114	56	F	3	Chlor.	36	10	7		1:800	-	1:50	Nil	1:25	Nil	1:25	Nil	
228	57	M	1	Chlor.	27	9	0		1:400+	-	1:400	-	1:400	-	1:800	Nil	Inoculated
119	57	F	2	Chlor.	29	8	5		1:200	-	1:25	Nil	Nil	Nil	Nil	Nil	
120	57	F	2	Chlor.	23	14	11		1:100	P.1:200	1:25	Nil	Nil	Nil	Nil	Nil	
141	57	F	3	Chlor.	22	7	2		Nil	P.1:100	Nil	Nil	Nil	Nil	Nil	Nil	
235	57	F	1	Chlor.	26	1	0		1:100	-	1:50	Nil	Nil	Nil	Nil	1:200	
457	58	M	3	Chlor.	19	10	9	Amp.	1:800	-	1:400	Nil	1:400	Nil	1:200	Nil	Excreter
415	58	F	3	Chlor.	28	5	6	L.T. Amp.	Nil	P. Nil	1:800	1:25	1:400	Nil	1:200	1:200	Excreter; relapsed

4. DETAILS OF 295 PATIENTS WHO SHOWED A "NORMAL" ANTIBODY RESPONSE (CONTD.) - PAGE 5

No.	AGE	SEX	SEVERITY OF ILLNESS	INITIAL TREATMENT: ANTIBIOTIC	INITIAL TREATMENT: DAILY DOSE MG/KG	DURATION OF CLINICAL ILLNESS BEFORE TREATMENT (DAYS)	DURATION OF PYREXIA ON TREATMENT (DAYS)	SUBSEQUENT TREATMENT	LEVELS OF AGGLUTINATION TITRES: ADMISSION 'H'	ADMISSION 'O'	DISCHARGE 'H'	DISCHARGE 'O'	3 MONTHS 'H'	3 MONTHS 'O'	6 MONTHS 'H'	6 MONTHS 'O'	REMARKS
129	59	M	3	CHLOR.	16	7	4	L.T.AMP.	1:200	NIL;P.1:25	NIL	NIL	NIL	NIL	NIL	NIL	EXCRETER;INOCULATED
409	59	F	3	CHLOR.	25	15	3		1:200	NIL;P.1:200+	-	-	1:100	NIL	1:100	NIL	
56	59	F	3	CHLOR.	19	5	7		1:1280	NIL;P.1:100	1:400	NIL	-	1:25	1:25	NIL	
106	59	F	2	CHLOR.	27	6	3	AMP. CHLOR. LT	NIL	-	1:400	NIL	1:50	NIL	1:25	1:25	RELAPSED
345	60	M	2	CHLOR.	24	14	6	CHLOR;CHLORTET;AMP.	NIL	-	1:200	NIL	-	-	-	-	EXCRETER;RELAPSED
444	60	F	1	AMP.	66	10	0		1:200	-	NIL	NIL	NIL	NIL	-	-	
124	60	F	3	CHLOR.	39	4	6		1:100	-	1:50	NIL	NIL	NIL	NIL	NIL	
207	60	F	3	CHLOR.	44	2	7	METHAC.	1:25	NIL	1:100	NIL	NIL	NIL	NIL	NIL	EXCRETER
177	61	M	2	CHLOR.	27	0	9	AMP.	1:400	-	1:800	NIL	1:25	NIL	1:25	NIL	EXCRETER
41	61	F	3	CHLOR.	45	0	6	L.T. AMP.	1:400+	-	-	-	1:25	NIL	1:800	1:50	EXCRETER
351	62	M	2	CHLOR.	24	12	4	CHLOR;CHLORTET.	1:500	P.1:100	1:400	NIL	1:50	NIL	NIL	NIL	RELAPSED
238	62	M	3	CHLOR.	28	6	4		1:100	-	1:25	NIL	NIL	NIL	NIL	NIL	
48	62	F	2	CHLOR.	27	9	5	CHLOR; AMP;L.T.AMP	1:100	-	1:400	NIL	1:50	NIL	1:200	NIL	RELAPSED;CARRIER
200	62	F	3	CHLOR.	30	2	5		1:50	-	1:200	-	NIL	NIL	NIL	NIL	
368	62	F	2	CHLOR.	19	18	3	L.T.AMP.	NIL	P.1:200+	1:50	NIL	1:50	NIL	1:100	NIL	EXCRETER
239	62	F	2	CHLOR.	28	23	1	CHLOR.L.T.AMP.	1:320	NIL	1:3200	1:25	1:200	NIL	1:200	1:50	EXCRETER
440	63	M	2	CHLOR.	29	10	3		1:640	-	NIL	NIL	NIL	NIL	NIL	NIL	
359	63	F	3	CHLOR.	38	8	3		1:100	P.1:200+	1:800	-	1:400	NIL	1:50	1:50	
281	63	M	3	CHLOR.	31	11	9		1:800	1:25	1:400	-	1:100	1:50	NIL	NIL	INOCULATED
44	64	F	2	CHLOR.	28	23	1	CHLOR.L.T.AMP.	1:320	NIL	1:3200	1:25	1:200	NIL	1:200	1:50	EXCRETER
240	65	F	2	CHLOR.	35	17	5		1:100	-	NIL	NIL	-	-	NIL	1:50	
535	65	M	2	CHLOR.	27	0	15	AMP.	1:400	NIL	1:1600	-	1:1600	-	1:3200	1:200	INOCULATED;RELAPSED
286	65	M	1	CHLOR.	26	7	0		1:400	-	1:1600	-	1:1600	-	1:400	1:25	INOCULATED
287	65	M	0	CHLOR.	29	6	4		1:400	-	1:3200	NIL	-	-	-	-	INOCULATED 1914
198	65	F	1	AMP.	33	11	9		1:25	P.1:100	1:50	-	NIL	NIL	1:25	NIL	
162	66	M	1	CHLOR.	21	7	0	CHLOR.	1:50	P. NIL	1:50	NIL	1:100	NIL	1:50	1:50	INOCULATED
355	67	M	1	CHLOR.	20	17	0		1:100	NIL;P.1:25	1:400	NIL	1:400	NIL	1:100	1:50	INOCULATED
403	67	F	2	CHLOR.	32	10	4	AMP. L.T.AMP.	1:100	-	NIL	NIL	1:400	NIL	1:100	1:100	EXCRETER;RELAPSED
105	68	F	2	CHLOR.	21	9	5	AMP.	1:400	-	1:6400	1:50	1:1600	-	1:50	NIL	EXCRETER; INOCULATED 1964
218	68	F	1	CHLOR.	20	0	0		1:320	-	1:25	NIL	1:25	NIL	1:25	NIL	
111	69	F	2	CHLOR.	40	13	4	CHLOR.	1:200	-	NIL	NIL	NIL	NIL	-	-	RELAPSED
538	69	F	3	CHLOR.	34	8	2	AMP.CHLOR.L.T.AMP	1:1600	NIL	1:1600	NIL	-	-	-	-	EXCRETER+RELAPSED
245	69	F	2	CHLOR.	21	25	3	CHLOR.CHLORTET;LT.AMP	1:400+	-	1:1600	NIL	1:400	NIL	1:200	NIL	EXCRETER
428	69	F	3	CHLOR.	26	5	14	AMP. L.T.AMP.	1:50	NIL	1:200	NIL	1:50	NIL	NIL	NIL	EXCRETER;RELAPSED
55	69	M	3	CHLOR.	27	6	11	CHLOR.	1:400	-	1:200	-	1:100	-	-	-	INOCULATED;RELAPSED
80	79	M	1	CHLOR.	29	7	1		1:25	-	1:25	NIL	1:100	NIL	1:50	NIL	INOCULATED.
524	70	M	2	CHLOR.	29	11	2	CHLOR;METHAC;ACHRO; CEPHALOSP.	1:50	-	1:800	NIL	1:200	NIL	1:100	1:25	INOCULATED;CARRIER
311	70	M	2	AMP.	35	7	2		1:200	-	1:100	-	-	-	-	-	INOCULATED
360	72	F	3	CHLOR.	35	8	9	CHLOR.	NIL	P.1:100	1:200	1:50	1:50	P.1:25	-	-	RELAPSED
410	73	F	3	CHLOR.	29	14	3		1:100	NIL;P.1:50	1:200	NIL	1:50	NIL	1:25	-	INOCULATED
188	75	F	1	MIXED		5	10		1:50	-	1:400	1:100	1:25	NIL	NIL	1:50	
537	74	M	2	MIXED		10	14	AMP.	1:200	-	1:25	NIL	NIL	NIL	NIL	NIL	RELAPSED
178	75	M	1	CHLOR.	21	20	1		1:2000+	NIL	1:800	NIL	1:1600	NIL	1:800	NIL	INOCULATED
258	75	M	3	CHLOR.	22	9	10		1:250	NIL; 1:50P	1:25	NIL	NIL	NIL	-	-	
147	75	F	1	CHLOR.	35	3	3		1:400	-	1:50	NIL	NIL	NIL	NIL	NIL	
140	76	M	2	CHLOR.	19	20	7		1:100	-	1:100	NIL	1:100	NIL	1:100	1:100	INOCULATED
523	76	F	3	CHLOR.	39	0	5	L.T.AMP.	1:400+	-	-	-	-	-	1:50	NIL	EXCRETER;RELAPSED
477	77	F	1	CHLOR.	41	17	2		-	P.1:250	NIL	NIL	1:50	1:50	-	-	
58	79	F	3	CHLOR.	39	9	3		1:200	-	1:200	NIL	NIL	NIL	-	-	
361	81	F	3	CHLOR.	24	2	5		1:1280	P.NIL	1:1600	-	1:100	-	1:25	NIL	
89	91	F	2	CHLOR.	32	7	7		1:200	-	1:25	NIL	-	-	-	-	

CHLOR. = CHLORAMPHENICOL AMP. = AMPICILLIN METHAC = METHACYCLINE
CHLORTET. = CHLORTETRACYCLINE. L.T.AMP. = LONG-TERM AMPICILLIN. ACHRO. = ACHROMYCIN
CEPHALOSP. = CEPHALOSPORIN

1. Comparison of the Age Distribution of Convalescent Excreters and other Typhoid Patients

Age (years)	Convalescent Excreters	All Others	Totals
0 - 14	50 (37)	58 (71)	108
15 - 29	41 (43)	85 (83)	126
30 - 44	25 (25)	50 (50)	75
45 - 59	25 (29)	61 (57)	86
60 & over	18 (25)	56 (49)	74
ALL AGES:	159	310	469

$\chi^2 = 9.68$ D.F. = 4 $P < 0.05$ - possibly significant

2. Comparison of the Incidence of Inoculated Adults in Convalescent Excreters and other Adult Typhoid Patients

See Appendix to Section IV (3)

3.(A)

COMPARISON OF CONVALESCENT EXCRETERS AND OTHER PATIENTS ON THE BASIS OF THE SEVERITY OF THE INITIAL INFECTION

SEVERITY:	0 + 1	2 + 3	TOTALS
CONVALESCENT EXCRETERS	20 (37)	139 (122)	159
ALL OTHER CASES	89 (72)	221 (230)	310
TOTAL:	109	360	469

$\chi^2 = 15.33$ D.F. = 1 P < 0.00050 ~ HIGHLY SIGNIFICANT

3.(B)

COMPARISON OF CONVALESCENT EXCRETERS AND OTHER PATIENTS ON THE BASIS OF THE SEVERITY OF THE INITIAL INFECTION DISTINGUISHING AGE-GROUPS

AGE:	0 - 14		15 - 29		30 - 44		45 - 59		60 & OVER	
SEVERITY:	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3	0+1	2+3
CONVALESCENT EXCRETERS	7	43	3	38	5	20	4	21	1	17
OTHERS	10	48	19	66	18	32	21	40	21	35
TOTAL:	17	91	22	104	23	52	25	61	22	52

0 - 14 YEARS)
15 - 29)
30 - 44) NO DIFFERENCE
45 - 59)
60 & OVER $\chi^2 = 5.21$ D.F. = 1 P < 0.05

60 & OVER :

SEVERITY:	0 + 1	2 + 3	TOTALS
CONVALESCENT EXCRETERS	1 (5)	17 (13)	18
OTHERS	21 (17)	35 (39)	56
ALL 60 & OVER	22	52	74

$\chi^2 = 5.21$ D.F. = 1 P < 0.05 ~ POSSIBLY SIGNIFICANT.

ABERDEEN TYPHOID OUTBREAK, 1964

PATTERN OF EXCRETION OF 6 POSSIBLE CHRONIC CARRIERS

No. 72 F.34 WT. 71 KG.	TIMING: TREATMENT: STOOL: URINE:	2 WEEKS x 2 CHLOR. POS. INTERMITTENTLY POSITIVE	4 WEEKS	2 WEEKS METHAC. NEG.	12 WEEKS POS.	6 WEEKS METHAC. NEG.	4 WEEKS POS.	4 WEEKS CEPH.	10 WEEKS	6 MONTHS NEG. →	
No.531 F.46 WT. 90 KG.	TIMING: TREATMENT: STOOL:	2 WEEKS CHLOR. POS.	10 DAYS AMP. NEG.	2 WEEKS POS.	13 WEEKS AMP. NEG.	1 WEEK POS.	6 WEEKS AMP. + METHAC. NEG.	4 WEEKS POS.	12 WEEKS AMP. + PROBENECID NEG.	4WEEKS INTERMITTENTLY POS.	5 MONTHS CONSTANTLY POSITIVE
No.113 M.53 WT. 69 KG. TAB.1945	TIMING: TREATMENT: STOOL:	2 WEEKS CHLOR. POS.	4 WEEKS	13 WEEKS AMP. NEG. (1 POS. SPECIMEN)	6 WEEKS POS.	6 WEEKS AMP. + METHAC NEG.	4 WEEKS POS.	12 WEEKS AMP. + PROBEN. INTERMITTENTLY POS.	7 MONTHS POS.		
No.48 F.62 WT.72 KG.	TIMING: TREATMENT: STOOL:	2 WEEKS x 2 CHLOR. POS.	10 DAYS AMP. NEG.	3 WEEKS POS.	13 WEEKS AMP. NEG.	3 WEEKS	16 WEEKS NOT TESTED	12 WEEKS INTERMITTENTLY POS.	14 WEEKS CONSTANTLY POSITIVE		
No.291 F.67 WT. 76 KG.	TIMING: TREATMENT: STOOL:	2 WEEKS CHLOR. POS.	1 WEEK AMP. NEG.	6 WEEKS	13 WEEKS INTERMITTENTLY POS.	6 WEEKS METHAC. NEG.	4 WEEKS POS.	4 WEEKS CEPH. NEG.+POS.	9 MONTHS		
No.524 M.70 WT. 72 KG.	TIMING: TREATMENT: STOOL:	2 WEEKS x 2 CHLOR. POS.	4 WEEKS NEG.POS.	2 WEEKS METHAC. NEG.	3 MONTHS POS.	6 WEEKS ACHROMYCIN NEG.	4 WEEKS POS.	4 WEEKS CEPH. INTERMITTENTLY POS.	8 WEEKS	8 MONTHS CONSTANTLY POS.	

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REFERENCES

(The figures in the final brackets refer to pages in the present thesis)

ACHARD, C. & BENSAUDE, R. (1896) "Infections Paratyphoidiques". Bull. Soc. Méd. Hôp. Paris (13) 820 (12)

AHUYA, M. L. (1957) "Prophylactic Value of Typhoid Vaccine". Lancet (i) 1199 (158)

ANDERSON, E. S. (1965) Personal Communication. (91)

& GUNNELL, Anne (1964) "A Suggestion for a New Anti-Typhoid Vaccine". Lancet (ii) 1196 (196)

& RICHARDS, H. G. H. (1948) "An Outbreak of Typhoid Fever in the Middle East". J. Hyg. (46) 164 (157,175)

ANDERSON, T. (1964) "The Treatment of Acute Infections Diseases - The Typhoid Carrier". Practitioner (193) 483 (230,232)

ARCHER, G. T. & WHITBY, J. L. (1957) "Protection of Mice by Living Vi and O Vaccines against Death caused by Salmonella Paratyphi C". J. Hyg. (55) 513 (11)

ARKWRIGHT, J. A. (1921) "Variations in Bacteria in Relation to Agglutination both by Salts and by Specific Serum" J. Path. Bact. (24) 35 (11,145)

(1927) "The Value of Different Kinds of Antigen in Prophylactic Enteric Vaccines". Ibid. (30) 345 (145)

ASCHOFF, L. (1924) "The Reticulo-Endothelial System". Ergebn. Inn. Med. Kinderheilk (26) 1 (43)

ASHCROFT, M. T., MORRISON, Ritchie J. & NICHOLSON, C. C. (1964) "Controlled Field Trial in British Guiana Schoolchildren of Heat-killed Phenolised and Acetone-killed Lyophilised Typhoid Vaccines". Amer. J. Hyg. (79) 196 (61, 78, 175)

BARR, M., SAYERS, M.H.P. & STAMM, W. P. (1959) "Intradermal T.A.B.T. Vaccine for Immunisation against Enteric". Lancet (i) 816 (150)

BATTLEHNER, R. (1910) "Uber Latenz von Typhusbacillen im Menschen". Diss. Strassburg. (184)

BAUER, F. K. & BOWER, A. G. (1951) "Typhoid Fever of Short Duration". Amer. J. Med. Sci. (222) No.2 174 (77)

BEHRING, E. A. von & KITASATO, S. (1890) "Ueber das Zustandekommen der Diphtherie - Immunität und der Tetanus-Immunität bei Thieren". Deutsch. Med.Wschr (16) 1113 (42)

BELL, A. E. (1949) "Physiological Factors Associated with Genetic Resistance to Fowl Typhoid" J. Infect. Dis. (85) 154 (45)

BELL, D. (1937) "The Specific Treatment of Typhoid Fever" M.D. Thesis, Edinburgh. (18, 32, 33)

BENAVIDES, L. V., OLSEN, B. H. & VARELA, G. M. C., HOLT, S. H. (1955) "Treatment of Typhoid with Synnematin B; Preliminary Report" J.A.M.A. (157) 989 (19)

BENENSON, A. S. (1964) "Serological Responses of Man to Typhoid Vaccines" Bull. W.H.O. (30) 653 (164)

BENSTED, H. J. (1958) "Colony Variation and Mouse Virulence of Typhoid Bacilli" Bull. Research Council of Israel, 7E No.1 (2) 25 (145)

BERSCH, E. (1926) "Zur Pathologie und Therapie der Typhusbazillentrager" Med. Klin. Berl. (22) 409 (220)

BESREDKA, A. (1902) "Active Immunisation against Plague, Cholera and Typhoid Infections" Ann. Inst. Pasteur (16) 918 (18,144)

(1927) "Local Immunisation" London (38,146)

BHATNAGAR, S. S., SPEECHLY, C. G. & SINGH, M. (1938) "A Vi Variant of Salmonella Typhi and its Application to the Serology of Typhoid Fever" J. Hyg. (38) 663 (10)

BOYD, J. S. K. (1943) "Enteric Group Fevers in Prisoners-of-War from Western Desert with Special Reference to Prophylactic Immunisation" Brit. Med. J. (1) 719 (156)

(1943) "Immunisation against Enteric Group Fevers" Ibid. (ii) 178 (156)

BRETONNEAU, P. F. (1829) "Notice Sur la Contagion de la Dothiénentérite" Arch. Gén. de Méd. (21) Sér.1 57 (3)

BRODIE, J. & DAVIDSON, W.A. (1944) "Observations on an Epidemic of Paratyphoid Fever in Dundee 1941" J. Hyg. (43) 219

BROWN, D. M. (1964) "Tissue Distribution of Penicillins" Postgrad. Med. J. Supp. (40) 31 (231)

BROWNING, C. H., COULTHARD, H. L., CRUICKSHANK, R., GUTHRIE, K. G. & SMITH, R. P. (1933) "Chronic Enteric Carriers and Their Treatment" M.R.C. Special Report Series No.179. H.M.S.O., London (214, 215, 219, 221, 223)

BRUMFITT, W. (1964) "Therapy with the New Penicillins" Postgrad. Med. J. Supp. (40) 94 (231)

BUDD, W. (1856) "On the Fever at the Clergy Orphan School, St. John's Wood" Lancet (ii) 618, 694. (7, 8, 9

(1873) "Typhoid Fever: Its Mode of Spreading and Prevention" London (8, 9, 1 76)

BULLOCK, W. E. (1963) "Ampicillin Therapy of Salmonella Carriers: A Summary of Laboratory and Clinical Observations" Amer. J. Med. Sci. (246) 42 (20, 96, 232)

BUMKE, E. (1925) "Niere und Typhus Beobachtungen an Typhus - Paratyphus A- und B- Urinausscheidern" Virchow Arch. Path. Anat. (256) 446 (223)

CASTELLANI, A. (1909) "Observations on Typhoid Vaccination in Man with Attenuated live Cultures" Centralbl. f. Bakt. (52) 92 (144)

CHANTEMESSE, A. (1891) "Fièvre Typhoïde. Traité de Méd." Thèse de Paris (1) 687 (12, 214

(1898) "Toxine Typhoïde Soluble et Serum Antitoxique de la fièvre Typhoïde" Progres. Méd. (7) 245 (18)

CHOMEL, A. F. (1836) "Lectures of the Medical Clinic Typhoid Fever" Collected and published by J. L. Genest, Paris 1834. Brit. & Foreign M. Rev. (2) 33 (3)

CHRISTIE, A. B. (1964) "Treatment of Typhoid Carriers with Ampicillin" Brit. Med. J. (i) 1609 (20, 231 96)

CLIMIE, H. (1942) "Immunization against Typhoid and Paratyphoid with Alcohol-killed, Alcohol-preserved and Heat-killed, Phenol-preserved, Vaccine" J. Hyg. (42) 411 (159)

COCKBURN, W. C. (1955) "The early History of Typhoid Vaccination" J. Roy. Army M. Corps (101) 171 (154)

COOKSON, H. & FACEY, R. V. (1937) "Value of a Specific Serum in the Treatment of Typhoid Fever" Brit. Med. J. (i) 1009 (18)

COONS, A. H., LEDUC, E. H. & CONELLY, J. M. (1955) "Studies on Antibody Production II The Primary and Secondary Responses in the Popliteal Lymph Node of the Rabbit" J. Exp. Med. (102) 49 (45,147)

CONRADI, H. (1907) "Zur Frage der Ragionaren Typhusimmunität" Klin. Jahrb. (17) 273 (187)

CONRADI, J. (1907) "Wann Steckt der Typhuskranke an" Deutsch Med. Wschr. (33) 1684 (183)

CRAIGIE, J. & BRANDON, K. F. (1936) "Bacteriophage Specific for the O-Resistant Forms of B. Typhosus" J. Path. Bact. (43) 233 (11)

(1936) "The Identification of the V and W forms of B. Typhosus and the Occurrence of the V form in Cases of Typhoid Fever and Carriers" Ibid. 249 (11)

CRAIGIE, J. & YEN, C. H. (1938) "Demonstration of Types of B. Typhosus by means of Preparations of Type II Vi Phage: Principles and Techniques" Canad. J. Pub. Health (29) 448 (11)

(1938) "Demonstration of Types of B. Typhosus by means of Preparations of Type II Vi Phage: Stability and Epidemiological Significance of V forms of B Typhosus." Ibid. 484 (11)

CVJETANOVIC, B. & UEMURA, K. (1965) "The present Status of Field and Laboratory Studies of Typhoid and Paratyphoid Vaccines: With special reference to Studies sponsored by The World Health Organisation" Bull. W.H.O. (32) 29 (165)

DAWSON, A., D.P.H., O.B.E. (1965) Personal Communication (14)

DEAVER, J. B. & PFEIFFER, D. (1914) "Chronic Pancreatitis" Ann. Surg. (59) 841 (221)

DEHLER, A. (1907) "Zur Behandlung der Typhusbacillenträger" Munchen. Med. Wschr. (779) 2134 (20, 21

(1912) "Zur Behandlung der Typhusbacillenträger" Munchen. Med. Wschr (59) i 857 (20)

DOAN, C. A. (1940) "Reticulo-Endothelial System: Its Physiology and Pathology" J. Lab. Clin. Med. (26) 89 (45)

DRIGALSKI, W. von (1904) "Ueber Ergebnisse Bei der Bekämpfung des Typhus" Centralbl. f. Bakt. (35) 776 (38)

& CONRADI, H. (1902) "Ueber ein Verfahren zum Nachweiss der Typhusbacillen" Ztschr. f. Hyg. U. Infektionskr (39) 283 (13, 184 214)

DRYSDALE, A. (1947) "Comparative Study of Phenolized and Alcoholized T.A.B. Vaccines" J. Hyg. (45) 46 (159)

DUPRE, A. (1891) "Les Infections Biliares" Paris (214)

EBELING, E. (1914) "Ueber das Vorkommen von Typhusbacillen im Blut Eines 'Gesunden" Bacillenträgers" Berl. Klin. Wschr. (51) 689 (187)

EBERTH, C. J. (1880) "Die Organismen in den Organen bei Typhus Abdominalis" Arch. f. Path Anat. Berl. (81) 58 (9)

EDSALL, G., CARLSON, M.C., FORMAL, S.B. & BENENSON, A. S. (1959) "Laboratory Tests of Typhoid Vaccines Used in a Controlled Field Study" Bull. W.H.O. (20) 1017 (162)

EL RAMLI, A. H. (1953) "Chloramphenicol in Typhoid and Paratyphoid Fevers. New Lines of Treatment" Lancet (i) 927 (112, 11 115)

EL RGOBY, A. & GOHAR, M. A. (1956) "The Effect of Chloramphenicol on Agglutination Titre in Enteric Fevers" J.Trop.Med (59) 47 (116)

EPIDEMIOLOGICAL AND VITAL STATISTICS REPORT (1964) (17) 403 W.H.O. New York (Tables 4, 5)

ERLIK, D. & REITLER, R. (1960) "Intrahepatic Typhoid Infection as Cause of the Carrier State" Lancet (i) 1216 (20,216, 220, 2

FAVORITE, G. O. & MORGAN, H. R. (1942) "Effects Produced by the Intravenous Injection in Man of a Toxic Antigenic Material derived from Eberthella Typhosa" J. Clin. Invest. (21) 589 (41)

FELIX, A. (1924) "The Qualitative Receptor Analysis in its Application to Typhoid Fever" J. Immun. (9) 115 (10, 155

(1930) "Qualitative Serum Diagnosis of Enteric Fevers: Directions for its Performance" Lancet (i) 505 (63, 195 196,197 198)

(1935) "Clinical Trials with a New Antityphoid Serum" Ibid. (i) 799 (18,33)

(1941) "A New Type of Typhoid and Paratyphoid Vaccine" Brit. Med. J. (i) 391 (15, 143, 150, 155, 159)

& PITT, R. Margaret (1934) "Virulence of B. Typhosus and Resistance to O Antibody" J. Path. Bact. (38) 409 (18)

(1934) "New Antigen of B. Typhosus; Its Relation to Virulence and to Active and Passive Immunisation" Lancet (ii) 186 (18)

(1951) "The Pathogenic and Immunogenic Activities of Salmonella Typhi in Relation to its Antigenic Constituents" J. Hyg. (49) 92 (11, 155)

RAINSFORD, S. G. & STOKES, E. J. (1941) "Antibody Response and Systemic Reactions after Inoculation of New Type of T.A.B.C. Vaccine" Brit. Med. J. (i) 435 (16, 155, 159)

FERGUSON, T. (1958) "Scottish Social Welfare 1864-1914" Edin. and Lond. (26, 34, Table 6)

FLETCHER, W. (1918) "Report on the Bacteriological Examination of Soldiers Convalescent from Diseases of the Enteric Group" J. Roy. Army M. Corps (30) 51 (169)

FLINT, A. (1852) "Clinical Reports on Continued Fever" Buffalo (7)

FORBES, J. A. (1963) "The Treatment of Typhoid Fever" National Health and Medical Research Council of Australia Special Report Series No.6, 2nd Edit. 112 (113,115)

FORNET, W. (1912) "Statistisches uber den Typhus und die Typhusbekampfung im Südwesten des Reichs" Arb. kais. Ges. (41) 448 (185)

FORSTER, J. & KAYSER, H. (1905) "Ueber das Vorkommen von Typhusbacillen in der Galle von Typhuskranken, und Typhusbacillenträgern" Munchen Med. Wschr (52) I 1473 (186)

FOURRIER, A. & ROCCHICIOLI, P. (1963) "Modifications of Immunity in Cases of Typhoid Fever Treated with Chloramphenicol: The Problem of Relapse" Lille Med. (8) 507 (113, 114

FRAENKEL, E. (1893) "Ueber Spezifische Behandlung des Abdominaltyphus" Deutsch Med. Wschr. (19) 985 (18)

GAFFKY, G. (1884) "Zur Aitiologie des Abdominaltyphus" Mitt. A. D. Kais. Ges. (ii) 372 (9, 220)

GARBAT, A. L. (1922) "Typhoid Carriers and Typhoid Immunity" Monographs of the Rockefeller Institute for Medical Research (16) (20, 214-218, 222 239)

GAY, F.P. (1918) "Typhoid Fever" New York (6,18,19, 76,143,14 199)

GENDRON (1834) "Dothiénenteries Observées aux Environs de Château du Loir" Arch. Gén. de Méd. (18) Sér. 1 (6)

GERHARDT, W. W. (1837) "On the Typhoid Fever which occurred in Philadelphia in the Spring and Summer of 1836" Amer. J. Med. Sci. (19) 289 (5)

GILBERT, A. & GIRODE, J. (1890) "Contribution à L'Etude Bacteriologique des Voies Biliares" Semaine. Méd. (10) 481 (10)

GILCHRIST, E. (1734) "Essay on Nervous Fevers" Edinb. Med. Essays and Observations 4 (2)

GLENNY, A. T. (1925) "Diphtheria Antitoxin in the Blood of Normal Horses" J. Path. Bact. (28) 241, 252, 305 (152)

GOEBBEL (1914) "Bericht Uber das Sektionsergebnis bei zwei Chronischen Typhusbazillenträgern" Ztschr. f. Hyg. u Infektionsk. (78) 555

GOODPASTURE, E. W. (1937) "Concerning Pathogenesis of Typhoid Fever" Amer. J. Path. (23) 175 (44)

GRASSET, E. (1945) "Statistical Results of 10 Years of Typhoid Endotoxin Immunisation in Witwatersrand Goldmines 1934-43 Publ. S. Afr. Nat. Med. Research (9) 163 (156)

& GORY, M. (1927) "Vaccination, Hyperimmunisation et Sérothérapie Antityphoidique Expérimentale, au moyen des Autolysats Formolés" C.R. Soc. & Biol. Paris (97) 1211 (144)

GRAY, A. L. (1938) " The Probable Typhoid Carrier Incidence in Mississippi" Amer. J. Pub. Health (28) 1415 (215)

GREISMAN, S. E., HORNICK, R. B., CAROZZA, F. A. Jnr. & WOODWARD, T. E. (1963) "The Role of Endotoxin During Typhoid Fever and Tularaemia in Man. Acquisition of Tolerance to Endotoxin" J. Clin. Invest. (42) 1064 (41)

GRIMME, C. (1908) "Ein unter dem Bilde der Weilschen Krankheit Verlaufender Fall von Typhus Abdominalis, Entstanden durch Autoinfekion von der Gallenblase her" München Med. Wschr. (54) 1822 (215)

HARE, F. E. (1898) "The Cold Bath Treatment of Typhoid Fever" Lond. and New York (17)

HAY, M. (1908) "Report on the Origin and Spread of the Epidemic of Typhoid Fever in Peterhead 1907" Peterhead. (34)

(1912) "Report on the Outbreak of Typhoid Fever, 1912" Peterhead. (30, 34 35)

HEJFEC, L. B. (1965) "Results of the Study of Typhoid Vaccines in Four Controlled Field Trials in U.S.S.R." Bull.W.H.O. (32) 1 (164)

HENDERSON, D. W. (1939) "The Protective Value of the Vi and O Antibody in Relation to the Virulence of Strains of Bact. Typhosum" Brit. J. Exp. Path. (20) 1 (143)

HEWETT, C. (1826) "Cases showing the Frequency of Follicular Ulceration in the Mucous Membrane of the Intestines in Idiopathic Fevers" Lond. Med. & Phys. J. (August) 97 (3)

HILL, C. L. F., ARMSTRONG, J. V., McDONALD, C. K. & ALLOTT, E. N. (1950) "Treatment of Typhoid Fever with Chloramphenicol" Lancet (ii) 802 (110)

HOCHSTER, R. M. & QUASTEL, J. H. (1963) Metabolic Inhibitors. A comprehensive treatise. Vol II, p.42 New York & London (127)

HODGKINSON, R. (1954) "Blood Dyscrasias associated with Chloramphenicol" Lancet (i) 285 (67, 96)

HOPPS, Hope E., SMADEL, J. E., BERNHEIM, B. E., DANAUSKAS, J., & JACKSON, E. B. (1961) "Effect of Antibiotics on Intracellular Salmonella Typhi. II Elimination of Infection by Prolonged Treatment" J. Immun. (87) 162 (122, 123 124, 125 126)

HORTON-SMITH, P. (1899) "On the Respective Parts taken by the Urine and the Faeces in the Dissemination of Typhoid Fever" Lancet (i) 1346 (13)

HOUSTON, T. (1899) "On a case of Cystitis of 3 years Duration due to the Typhoid Bacillus" Brit. Med. J. (i) 78 (13)

HUCKSTEP, R. L. (1962) "Typhoid Fever and other Salmonella Infections" Edinb. & Lond. (19,110,1 119,156, 198)

HUEPPE, F. (1886) "In Remarks on Articles by Fodor and Wyssokowitch" Fortschr. d. Med. (4) 447 (9)

JENKIN, C. R. & ROWLEY, D. (1963) "Basis for Immunity to Typhoid in Mice, and the Question of Cellular Immunity" Bact. Rev. (27) 391 (46)

& AUZINS, I. (1964) "The Basis for Immunity to Mouse Typhoid. I. The Carrier State" Aust. J. Exp. Biol. Med. Sci. (42) 215 (45)

JENNER, W. (1849) "On the Identity or Non-identity of the Specific Cause of Typhoid, Typhus and Relapsing Fever" Med. Chir. Trans. (33) (5, 76)

(1849) "Typhus and Typhoid: An attempt to determine the Question of their Identity or Non-identity by an Analysis of their Symptoms and Post-mortem Appearances" Edin. Month. J. M. Sc. 1849-50 (9) 10 (5)

JOHN, A. T. & VINAYAGAM, U. S. (1952) "Effect of Interrupted Course of Chloramphenicol on Relapse Rate: Typhoid Fever" Lancet (ii) 757 (113)

JONES, A. C. (1951) "Hospital Outbreak of Typhoid Fever Bacteriological and Serological Investigations" J. Hyg. (49) 335 (183, 186, 197,24

JORDAN, J. & JONES, H. E. (1945) "Typhoid Fever in Immunised Personnel" Lancet (ii) 333 (156, 175)

KLEBS, E. (1880) "Der Ileotyphus eine Schistomycose" Arch. f. Exp. Path. u. Pharmakol. (12) 231 (9)

KLINGER, P. (1906) "Uber Typhusbacillenträger" Arb. a. d. Kais. Ges. (24) 91) (185)

(1909) "Epidemiologische Beobachtungen Bei der Typhusbekämpfung im Sudwesten Reichs" Ibid. (30) 584 (14, 183, 185)

KOCH, R. (1902) "Die Bekämpfung des Typhus" Veröffentl A.D. Militärsanitätswesen (II) 21 (13, 214)

KOENIGSFELD, H. (1915) "Ein neues Prinzip der Serumtherapie bei Infektionskrankheiten, mit besondere Beruchtsichtigung des Typhus abdominalis" Munchen. Med. Wschr. (8) 253 (18)

KOSTIC, A. (1963) "The Problem of Typhoid Fever with Negative Serological Reactions" Presse Méd. (71) 2489 (117, 195, 207)

LANDY, M. (1953) "Enhancement of Immunogenicity of Typhoid Vaccine by Retention of Vi Antigen" Amer. J. Hyg. (58) 148 (143, 162

LANTIN, P. T., GERONIMO, A. & CALILONG, V. (1963) "The Problem of Typhoid Relapse" Amer. J. Med. Sci. (245) 293 (110, 117, 199)

LAZARUS, A. (1895) "Die Elsner'sche Diagnose des Typhusbacillus und ihre Anwendung in der Klinik" Berl. Klin. Wschr. (32) ii 1068 (13, 214)

LEDINGHAM, A. & LEDINGHAM, J. C. G. (1908) "Typhoid Carriers" Brit. Med. J. (i) 15 (14, 35)

LEDINGHAM, J. C. G. & ARKWRIGHT, J. A. (1912) "The Carrier Problem in Infectious Diseases" New York (182, 215, 217, 255)

LEFF, S. (1957) "Recent Outbreaks of Infectious Diseases" Lond. (214)

LEURET, Dr. (1928) "Mémoire sur la Dothiénentérite à Nancy" Arch. Gén. de Méd. (18) Sér. 1 (6)

LINZ, R. (1953) "Sur le Mechanisme de L'Action de la Streptomycine. III Le Cas de Microbacterium Tuberculosis" Ann. Inst. Pasteur (85) 295 (122)

LISON, L. & SMULDERS, J. (1948) "Discriminating 'Athrocytes" in the Reticulo-endothelial System" Nature, London (162) 65 (43)

LOMBARD, H. P. (1836) "Observations suggested by a Comparison of the Post-mortem Appearances of Typhus Fever in Dublin, Paris and Geneva" Dublin J. M. Sc. (10) 17, 101 (4, 26)

LONGCHAMPT, J. & CARBONEL, J. (1950) "Sur une Statistique de 140 Cas de Fièvre Typho-Paratyphiques Traitées par la Chloromycetine" Bull. Soc. Méd. Hôp. Paris (66) 1248 (82, 116, 119)

LOUIS, P. C. A. (1829) "Recherches sur la Maladie connue sous ler Noms de Gastro-Entérite" Paris (3)

LUIPPOLD, G. F. (1944) "Typhoid Vaccine Studies: Intracutaneous versus Subcutaneous Vaccination for Initial Immunisation" Amer. J. Pub. Health (34) 1151 (150)

LURIE, M. B. (1942) "Studies on the Mechanism of Immunity: Tuberculosis" J. Exp. Med. (60) 247 (46)

McDERMOTT, W. (1958) "Microbial Persistence" Yale J. Biol. Med. 30 257

MADSEN, T. (1937) "Mechanism of Bacterial Infection" Commun. de L'Inst. Serother de l'etat Danois (26) 33 (38,40,14 191)

MANRIQUES, L., SALCEDO, M., BORGONO, J. M., MARZULLO, E., KRALJEVIC, R., PAREDES, L., VALDIVIESO, R. (1965) "Clinical Trials with Ampicillin in Typhoid Fever and Paratyphoid A" Brit. Med. J. (ii) 152 (97)

MARMION, D. E. (1952) "The Treatment of Typhoid Fever with Chloramphenicol: A Clinical Study of 330 Cases of Enteric Fever treated in Egypt" Trans. Roy. Soc. Trop. Med. Hyg. (46) 619 (19,73,77, 96,113,11 116,117,11 119,121,12 134,187)

NAYLOR, G. R. E. & STEWART, J. O. (1953) "Second Attacks of Typhoid Fever" J. Hyg. (51) 260 (158)

MATTEUCCI, W. V., SCHIMMEL, N. H. & BOGER, W. P. (1951) "Typhoid Fever: Chloramphenicol and the Problem of Relapse" Amer. J. Med. Sci. (222) 446 (113)

MARRIOTT, H. L.(1947) "Water and Salt Depletion" Brit. Med. J. (i) 245 (17)

MEDICAL OFFICERS OF HEALTH (1965) North-East of Scotland Personal communication (36)

METCHNIKOFF, E. (1887) "Sur La Lutte des Cellules de L'Organismes contre L'Invasion des Microbes" Ann. Inst. Pasteur (i) 321 (42)

& BESREDKA, A. (1911) "Recherches sur la Fièvre Typhoide Experimentale" Ibid. (25) 193 (144)

MORGAN, H. R. (1948) "Resistance to the Action of the Endotoxins of Enteric Bacilli in Man" J. Clin. Invest. (27) 706 (41)

MINISTRY OF HEALTH (1945) Monthly Bull. Ministry Health and Emergency Public Health Laboratory Services (4) 224, H.M.S.O. London (196, 253)

MOYNIHAN, B. G. A. (1903) "A Case of Typhoid Pancreatitis" Lancet (i) 1586 (221)

MUGGLETON, P. N., O'CALLAGHAN, C. H. & STEVENS, W. K. (1964) "Laboratory Evaluation of a New Antibiotic - Cephaloridine" Brit. Med. J. (ii) 1234 (98)

MURCHISON, C. (1873) "A Treatise on the Continued Fevers of Great Britain" London, 2nd Edit. (1, 2, 9, 22, Table 1)

NETER, E. (1950) "Observation on the Transmission of Salmonellosis in Man" Amer. J. Pub. Health (40) 929 (38)

NEUHAUS, R. (1886) "Nachweis der Typhusbazillen am Lebenden" Berl. Klin. Wschr. (23) 89 (9)

NEVA, F. A. & MORGAN, H. R. (1950) "Tolerance to the Action of Endotoxins of Enteric Bacilli in Patients Convalescent from Typhoid and Paratyphoid Fevers" J. Lab. Clin. Med. (35) 911 (41)

NICHOLLE, C., CONOR, A., CONSEIL, E. (1912) "De L'inoculation intraveineuse des Bacilles typhiques morts a l'homme" Compt. rend. Acad. Sciences (145) 1036 (148)

NICHOLS, H. J., SIMMONS, J. S. & STIMMEL, C.O. (1919) "Surgical Treatment of Typhoid Carriers" J.A.M.A. (73) 680 (217)

OAKBERG, E. F. (1946) "Constitution of Liver and Spleen as Physical Basis for Genetic Resistance to Mouse Typhoid" J. Infect. Dis.(78) 79 (45)

OLITZKI, A. L., GODINGER, D. & GERSHON ZIPPORA (1964) "The Uptake of Salmonella Typhi by Phagocytes and its Intracellular Viability" Path. Microbiol.(27) 175 (43, 44, 126, 128)

ØRSKOV, J. (1932) "Der Bakterielle Infektionsmechanismus" Acta. Path. Microbiol. Scand. Suppl. (ii) 10 (38,40)

JENSEN, K. A. & KOBAYASHI, K. (1928) "Studien über Breslauinfektion der Mäuse, speziell mit Rücksicht auf die Bedeutung des Retikulo-Endothelialgewebes" Ztschr. f. Immunitatsforsch u. Exper. Therap.(55) 34 (38, 39)

& LASSEN, H. C. A. (1930) "Die Bedeutung der Grösse der Primären Infektionsdosis bei Einigen Natürlichen Infektionen Experimentelle Untersuchungen" Ibid.(67) 137 (38, 40)

& MOLTKE, O. (1928) "Studien über den Infektions-Mechanismus bei Verschiedenen Paratyphus-Infektionen an Weissen Mäusen" Ibid. 59, 357 (38, 39 40)

PARISH, H. J. & CANNON, D. A. (1962) "Antisera, Toxoids, Vaccines and Tuberculins in Prophylaxis and Treatment" 6th Edit. Edin. & Lond. (148)

PARK, W. H. & WILLIAMS, A. W. (1925) "Pathogenic Organisms" New York (Table 35)

PATRICK, A. (1955) "The Enteric Fevers 1800-1920" Edin. (4)

PEASE, Phyllis E. (1965) "L-Forms, Episomes and Auto-Immune Disease." Edinburgh and London (226)

PERRY, R. (1836) "Observations on Continued Fever in the Glasgow Hospitals" Edin. Med. & Surg. J. (45) 64 (4, 22, 26)

PERRY, R. M. (1937) "Comparison of Typhoid "O" and "H" Agglutinin Responses following Intracutaneous and Subcutaneous Inoculation of Typhoid, Paratyphoid A. and B. Vaccine" Amer. J. Hyg. (26) 388 (149)

PERRY, H. M., FINDLAY, H. T. & BENSTED, H. J. (1933)
(a) "Antityphoid Inoculation; Role of Bacterium Typhosum, Strain Rawlings" J. Roy. Army M. Corps (61) 81 (145)

(b) "Antityphoid Inoculation; Observations on Variation of Bact. Typhosum in vivo" Ibid. 241 (145)

PETIT ET SERRES (1813) "Traité de la Fièvre Entéro-Mésentérique" Paris (2)

PFEIFFER, A. (1885) "Ueber den Nachweiss der Typhusbacillen im Darminhalt und Stuhlgang" Deutsch Med. Wschr.(ii) 500 (9)

PFEIFFER, R. & KOLLE, W. (1896) "Experimentelle Untersuchungen zur Frage des Schutzimpfung des Menschen gegen Typhus Abdominalis" Ibid. (12) 735 (15, 141)

PIEDVACHE (1850) "Recherches sur la Contagion de la Fièvre Typhoïde" Mém. de L'Acad. de Méd. (15) (7)

POKROVSKII, V. I. & BULKINA, I. G. (1960) "Course of Typho-Paratyphoid Diseases and their Antibiotic Therapy at the Present Time" Ter. Arkh. (32) 49 (112)

PROST, P. A. (1804) "Médicine Eclairée par L'Observation et L'Ouverture des Corps" Paris (2)

RAETTIG, H. (1944) "The Effects of Protective Inoculation given during the Incubation Period of Typhoid Fever" Deutsch. Med. Wschr. (70) 213 (Excerpta Med. 1950) (174)

(1950) "Die Bakteriologische und Serologische Typhusdiagnostik für Praxis und Klinik" Berlin Med. Ztschr. (i) 325 (177)

(1959) "Provokation einer Infektion durch Schutzimpfung" Zbl. Bakt. I. Abt. Orig. (174) 192 (178)

REGISTRAR GENERAL, ENGLAND & WALES Annual Statistical Reports 1900-64. (22 - 37)

SCOTLAND (1961) Annual Statistical Reports 1900-64: Census 1951 & 1961 (22-37)

REID, R. (1827) "Clinical Observations on the Epidemic Fever of 1826" Irish Trans. (5) 266 (17)

REPORT OF THE ANTITYPHOID COMMITTEE (1912) H.M.S.O., London (142, 143)

REPORT OF DEPARTMENTAL COMMITTEE OF ENQUIRY (1964) "The Aberdeen Typhoid Outbreak 1964)" H.M.S.O. Cmnd. 2542 Lond. (49, 51, 52)

REPORTS OF DEPARTMENT OF HEALTH FOR SCOTLAND. Annual Reports 1929-64. (22 - 37)

REPORTS OF MEDICAL OFFICER OF HEALTH, CITY OF ABERDEEN. Annual Reports 1901-64. (29, 36)

COUNTY OF ABERDEEN - Annual Reports 1901-64. (36)

REPORT OF SALMONELLA SUB-COMMITTEE OF THE NOMENCLATURE COMMITTEE. Int. Soc. Microbiol. J. Hyg. (34) 333 (199)

REPORT OF SUB-COMMITTEE OF THE ADVISORY BOARD FOR ARMY MEDICAL SERVICES (1905) J. Roy. Army Corps (4) 242 (142)

ROLINSON, G. N. & STEVENS, S. (1961) "Microbiological Studies on a New Broad-Spectrum Penicillin, 'Penbritin'" Brit. Med. J. (ii) 191 (20, 96

ROWLAND, H. A. (1961) "The Treatment of Typhoid Fever" J. Trop. Med. Hyg. (64) 101 (82, 98 114,115
"The Complications of Typhoid Fever" Ibid. 143 119, 1

ROWLEY, D., TURNER, K. J., & JENKIN, C. R. (1964) "The Basis for Immunity to Mouse Typhoid. 3 Cell-Bound Antibody" Aust. J. Exp. Bio. Med. Sci. (42) 237 (46)

ROUS, P. & JONES, F. S. (1916) "The Protection of Pathogenic Microorganisms by Living Tissue Cells" J. Exp. Med. (23) 601 (46, 12

RUYS, A. Charlotte (1948) "Bacteriological and Epidemiological Data on Typhoid Fever in Amsterdam" Amer. J. Pub. Health (38) 1219 (186)

SAPHIR, W., BAER, W. H. & PLOTKE, F. (1942) "Typhoid Carrier Problem: Report of Study of 110 Typhoid Carriers at Manteno State Hospital, Manteno, Ill." JAMA (118) 964 (218)

SAWYER, W. A. (1915) "The Efficiency of Various Antityphoid Vaccines" Ibid. (65) 1413 (221)

SAYERS, M. H. P. (1961) "Recent Developments in Anti-Enteric Vaccine in the British Army" M.D. Thesis, London (146, 15 152, 16

SCHACHTER, M. (1956) "Typhoid Fever in Pregnancy as a Cause of Neuropsychiatric Disorders in Infants: 3 cases" Rev. Esp. Paediat. (12) 665 (88)

SCHELLER, R. (1908) "Beitrage zur Typhusepidemiologie" Centralbl. f. Bakt. (46) 385 (184)

SCHOTTMULLER, H. & FRAENKEL, E. (1925) "Clinical, Pathological & Epidemiological Aspects of Cholecystitis from Typhoid" München. Med. Wschr. (72) 2150 (216)

SCHUTZE, H. (1941) "The Optimal Spacing of Vaccine Inoculations" J. Path. Bact. (53) 443 (152)

SCIOLI, C., GIUSTI, G. & BALESTRIERI, G. (1964) "Comparison of Ampicillin & Chloramphenicol in Treatment of Typhoid Fever" Postgrad. Med. J. (40) 87 (97)

SCOTT, H. H. (1915) "An Investigation into the Causes of the Prevalence of Enteric Fever in Kingston, Jamaica; with special reference to the Question of Unrecognized Carriers" Ann. Trop. Med. Parasit. (9) 239 (185)

SCOTT, J. L., FINEGOLD, S. M., BELKIN, G. A. & LAWRENCE, J. S. (1965) "A Controlled Double-blind Study of the Haematological Toxicity of Chloramphenicol" New. Eng. J. Med. (272) 1137 (76,114)

SEDAN, J. & HERMANN, R. (1924) "Typhoid Infection in Guineapigs" C.R. Soc. Biol. (90) 567 (38)

SEELIGER, H. & VORLAENDER, K. O. (1953) "Die Widal-Reaktion bei Typhus und Paratyphus unter Besonderer Berücksichtigung Chloromycetinbehandelter Fälle" Ztschr. f. Immunitätsforsch u. Exper. Therap. (110) 128 (116)

SEIDLER, L. (1961) "The Pathogenesis of Relapses in Enteric Fever" Ztschr. f. Ärztl. Fortbild. (55) 15 (110, 11

SHARP, A. A. (1963) "Chloramphenicol Induced Blood Dyscrasias" Brit. Med. J. (i) 735 (114)

SHOWACRE, J. L., HOPPS, Hope E., DU BUY, H. G. & SMADEL, J. E., (1961) "Effect of Antibiotics on Intracellular Salmonella Typhi. I. Demonstration by Phase Microscopy of Prompt Inhibition of Intracellular Multiplication" J. Immun. (87) 162 (123, 12 227)

SILER, J. F. & DUNHAM, G. C. (1939) "Duration of Immunity Conferred by Typhoid Vaccine; Results of Revaccination by Intracutaneous Injection of Typhoid Vaccine; Laboratory Staff, Army Medical School" Amer. J. Pub. Health (29) 95 (149)

SIMPSON, W. H. (1882) Paper read to Aberdeen Philosophical Society (28)

SLEET, R. A., SANGSTER, G. & MURDOCH, J. M. C. (1964) "Comparison of Ampicillin and Chloramphenicol in Treatment of Typhoid Fever" Brit. Med. J. (i) 148 (97)

SMADEL, J. E. (1963) "Intracellular Infection and the Carrier State" Science (44) 153 (229)

WOODWARD, T. E. & BAILEY, C. A. (1949) "Relation of Relapses in Typhoid to Duration of Chloramphenicol Therapy" JAMA (141) 129 (19,112)

SMICK, K. M., CONDIT, P. K., PROCTOR, R. L. & SUTCHEN, V. (1964) "Fatal Aplastic Anaemia. An Epidemiological Study of its Relationship to the Drug Chloramphenicol" J. Chr. Dis. (17) 899 (96)

SMITH, D. T. & MARTIN, D. S. (1948) Zinsser's Textbook of Bacteriology. New York (178)

SNYDER, J. M., HORNICK, R. B., McCRUMB, F. R., Jnr., MORSE, L.J., & WOODWARD, T. E. (1964) "Asymptomatic Typhoidal Bacteraemia in Volunteers" Antimicrob. Agents Chemother. (3)604 (41, 187, 192)

SPAUN, J. (1957) "Typhoid Vaccine. Vi Antigen and Vi Antibody" ACTA Path. Microbiol. Scand. Supp. 123 (156, 15

STEVENSON, C. S., GLASKO, A. J., GILLESPIE, E. C. & MAUNDER, J.B. (1951) "Treatment of Typhoid in Pregnancy with Chloramphenicol" J.A.M.A. (146) 1190 (88)

STEWART, A. P. (1840) "Some Considerations on the Nature and Pathology of Typhus and Typhoid Fever applied to the Solution of the Question of the Identity or Non-Identity of the two Diseases" Edin. Med. Surg. J. (54) 289 (4)

"Some Considerations on the Nature and Pathology of the Continued Fever of Edinburgh Ibid. (45) 64 (4)

STEWART, G. T. (1964.) "Therapy with the New Penicillins" Postgrad. Med. J. (40) (Supp.) 94 (232)

STROEBE, F. (1928) "Provokation Typhus" Z. Klin. Med.(108)752 (177)

SUTER, E. (1956) "Interaction Between Phagocytes and Pathogenic Micro-organisms" Bact. Rev. (20) 94 (43, 44

SUTTON, T. (1806) "Account of a Remittant Fever among the Troops in this Climate" Canterbury (3)

TOP, F. H. (1964.) "Communicable Infections & Diseases" London (197)

TORRENS, J. (1923) "Official History of the War, Medical Services; Diseases of the War (1) II" H.M.S.O. (65, 17

TRAFFORD, D. J. P., LILLICRAP, D. A., HOUSTON, J. C., MACLAREN, D. M., BARNES, R. D. S. & KNOX, R. (1962) "Ampicillin, a Broad-Spectrum Penicillin" Lancet (i) 987 (96)

TROY, Patricia (1964.) "Ampicillin for Typhoid Carriers" Brit. Med. J. (i) 1252 (20, 232

TUFT, L. (1931) "Active Immunisation against Typhoid Fever, with Particular Reference to an Intradermal Method" J. Lab. Clin. Med. (16) 552 (148)

(1940) "Further Studies of the Intracutaneous Method of Typhoid Vaccination" Amer. J. Med. Sci. (199) 84. (149)

YAGLE, E. M., ROGERS, S. (1932) "Comparative Study of Antibody Response after Various Methods of Administration of Mixed Typhoid Vaccine, with particular reference to Intradermal and Oral Methods" J. Infect. Dis. (50) 98 (148)

TULLY, J. G., GAINES, S. & TIGERTT, W. D. (1963) "Studies on Infection and Immunity in Experimental Typhoid Fever. IV. Role of H Antigen in Protection." Ibid. (112) 118 (164)

TYPHOID PANEL, U.K. DEPT. OF TECHNICAL CO-OPERATION (1964.) "A Controlled Field Trial of Acetone-Dried and Inactivated and Heat-Phenol-Inactivated Typhoid Vaccines in British Guiana" Bull. W.H.O. (30) 631 (16, 16

VILCHUR, A. I. (1887) "Etiology and Clinical Bacteriology of Typhoid Fever" Inaug. Diss. St. Petersburg. (10)

VLADOIANU, I. R., DIMACHE, G., ANTOHI, S., VLADOIANU, Constanta, & ZARMA, Ortansa (1965) "Laboratory Tests on the Effectiveness of Oral Vaccination of Young Children against Typhoid and Paratyphoid A & B" Bull. W.H.O. (32) 37 (147)

VOGELSANG, Th. M. (1950) "Typhoid and Paratyphoid B. Carriers and Their Treatment" Bergen (198, 21 218-22

& BOE, J. (1948) "Temporary and Chronic Carriers of Salmonella Typhi and Salmonella Paratyphi B" J. Hyg. (46) 252 (20, 21

VOSBURG, W. H. & PERKINS, Anna E. (1925) "The Surgical Treatment of Typhoid Carriers in the Gowanda State Hospital" Surg., Gyneo. & Obstet. (40) 404 (214)

WALKER, W. (1964) "Cephaloridine in Typhoid" Brit. Med. J. (i) 1529 (98, 99

& HUNTER, R. B. (1951) "Oral Administration of Procaine Penicillin with and without Benemid p (DI - n - Propylsulphamyl) Benzoic Acid" Lancet (ii)104 (96)

WATSON, K. C. (1957) "The Relapse State in Typhoid Fever treated with Chloramphenicol" Amer. J. Trop. Med. (6) No.1 72 (112, 1 122, 12

WATT. J. P. (1918-20) Unpublished Correspondence (29,35)

WEIBULL, C. (1955) The Isolation of Protoplasts from Bacillus Megaterium by controlled treatment with lysozyme J. Bact. 66 688 (226)

WEIL, E. & FELIX, A. (1917) "Weitere Untersuchungen über das Wesen der Fleckfieberagglutination" Wien. Klin. Wschr. (30) 1509 (10)

(1920) "Ueber den Doppeltyphus der Rezeptoren in der Typhus-Paratyphus-Gruppe" Ztschr. f. Immunitätsforsch u. Exper. Therap (29) 24 (10. 14 195)

WHIPPLE, A. O. (1929) "Surgical Treatment of Bile Typhoid Carriers" Ann. Surg. (90) 631 (20, 21

WHITBY, J. M. F. (1964) "Ampicillin in the Treatment of S. Typhi Carriers" Lancet (ii) 71 (232

WIDAL, F. (1896) "On the Sero-Diagnosis of Typhoid Fever" Lancet (ii) 1371 (10, 19

WILLIS, T. (1959) "De Febribus" Ed. 1682 London (2,6,22

WILSON, A. T. (1953) "Egestion of Phagocytized Particles by Leucocytes" J. Exp. Med. (98) 305 (43, 229

WILSON, G. S. & MILES, A. A. (1965) "Topley and Wilson's Principles of Bacteriology and Immunity" 5th Ed. Lond. (12,38,4 70,74,17 254)

WILSON, W. J. (1938) "Isolation of B. Typhosus by means of Bismuth sulphide medium in water and milk-borne epidemics" J. Hyg. (38) 507 (184)

WITTLER, R. G., CARY, S. G. & LINDBERG, R. B. (1956) "Reversion of a pleuro-pneumonia-like organism to a Corynebacterium during tissue culture passage" J. Gen. Microbiol. 14, 763 (227)

WOODWARD, T. E., HALL, H. E., DIAS-RIVERAR, HIGHTOWER, S. A., MARTINEZ, E. & PARKER, R. T. (1951) "Treatment of Typhoid Fever: Control of clinical manifestations with cortisone" Ann. Int. Med. (34) 10 (98)

SMADEL, J. E., LEY, H. L., GREEN, R. & MANKIKAR, D. S. (1948) "Preliminary Report on Beneficial Effect Chloromycetin in Treatment of Typhoid Fever" Ibid. (29) 131 (17, 19 96)

SMADEL, T. E. & LEY, H. L. (1950) "Chloramphenicol and Other Antibiotics in Treatment of Typhoid Fever and Typhoid Carriers" J. Clin. Invest. (29) 87 (134)

SMADEL, J. E. & PARKER, R. T. (1954) "The Therapy of Typhoid Fever" Med. Clin. N. Amer.(38)577 (112,113,

& SMADEL, J. E. (1964) "Management of Typhoid Fever and its Complications" Ann. Int. Med. (60) 144 (98,110,1 130)

WRIGHT, A. E. (1896) "Association of Serious Haemorrhages with Conditions of Defective Blood Coagulability" Lancet (ii) 807 (15, 141)

(1902) "Synopsis of the Results which have been obtained by the Anti-Typhoid Inoculations" Ibid. (ii) 651 (141, 174

(1904) "A Short Treatise on Antityphoid Inoculation" 1st Edit. Lond. (146, 177 178)

YUGOSLAV TYPHOID COMMISSION (1962) "A Controlled Field Trial of the Effectiveness of Phenol and Alcohol Typhoid Vaccines" Bull. W.H.O. (26) 357 (16, 161, 162)